Nevada Medicaid Drug Use Review Board Meeting

July 23, 2020

OPTUMRx®

Table of Contents

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	June 3, 2020
Date of Meeting:	Thursday, July 23, 2020 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).
Place of Meeting:	Please use the teleconference/WebEx options provided below. If accommodations are requested, please advise using the information at the end of this agenda. Out of deference to Declaration of Emergency Directive 006 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/Declaration-of-Emergency-Directive-006-re-OML.3-21-20.pdf) from the State of Nevada Executive Department signed by Governor Sisolak as well as Emergency Directive 003 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/2020-03-20.Declaration-of-Emergency-Directive-003.pdf) signed March 20, 2020, a physical location will not be open to the public for attendance at this time.

Note: If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email or call (information) and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.

Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=ed02abdc380bb79be7fdb72548e9a697c Or go to www.webex.com and enter the Event Number listed below. Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.
Event Number:	161 606 2888 Click "Join Now." Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet.

A password should not be necessary, but if asked use: Medicaid1!

For Audio Only:

Phone: 1-763-957-6300
Event: 161 606 2888

AGENDA

1. Call to Order and Roll Call

2. Public Comment on Any Matter on the Agenda

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from April 30, 2020.

b. Status Update by the DHCFP

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for psychotropic medications for children and adolescents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for fibromyalgia agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for osteoporosis agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for anti-lipidemic agents – PCSK9 inhibitors.

i. Public comment on proposed clinical prior authorization criteria.

ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for diazepam (Valtoco®) nasal spray.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for substance abuse agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for growth hormones.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

5. Public Comment on any DUR Board Requested Report

6. DUR Board Requested Reports

a. Opioid utilization – top prescribers and members.

i. Discussion by the Board and review of utilization data.
ii. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

7. Public Comment on any Standard DUR Report

8. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q4 2019 and Q1 2020 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q1 2020.

ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

i. Status of previous quarter.
ii. Status of current quarter.
iii. Review and discussion of responses.

9. Closing Discussion

a. Public comments on any subject. (Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (email address). There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).)

b. Date and location of the next meeting.

c. Adjournment.

PLEASE NOTE: **Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to five minutes.**

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov, as well as Carson City, Las Vegas, and Reno central offices for the DHCFP. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). At this time, in deference to Emergency Directive 006 dated March 22, 2020 and related directives which have discouraged certain in-person activities, notice has not been posted at other physical locations.

If you require a physical copy of supporting material for the public meeting, please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). Supporting material will also be posted online as referenced above.

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the DHCFP as soon as possible and at least ten days in advance of the meeting, by e-mail at tbenitez@dhcfp.nv.gov in writing,

at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 3: The requirements contained in NRS 241.020 (4)(a) that public notice agendas be posted at physical locations within the State of Nevada are suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 4: Public bodies must still comply with requirements in NRS 241.020 (4)(b) and NRS 241.020 (4)(c) that public notice agendas be posted to Nevada's notice website and the public body's website, if it maintains one along with providing a copy to any person who has requested one via U.S. mail or electronic mail.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 5: The requirement contained in NRS 241.020 (3)(c) that physical locations be available for the public to receive supporting material for public meetings is suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

Summary of the DUR Board

Drug Use Review Board

The Drug Use Review Board (DUR) is a requirement of the Social Security Act, Section 1927 and operates in accordance with Nevada Medicaid Services Manual, Chapter 1200 – Prescribed Drugs and Nevada Medicaid Operations Manual Chapter 200.

The DUR Board consists of no less than five members and no more than ten members appointed by the State Director of Health and Human Resources. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist.

The DUR Board meets quarterly to monitor drugs for:

- therapeutic appropriateness,
- over or under-utilization,
- therapeutic duplications,
- drug-disease contraindications
- quality care

The DUR Board does this by establishing prior authorization and quantity limits to certain drugs/drug classes based on utilization data, experience, and testimony presented at the DUR Board meetings. This includes retrospective evaluation of interventions, and prospective drug review that is done electronically for each prescription filled at the Point of Sale (POS).

Meetings are held quarterly and are open to the public. Anyone wishing to address the DUR Board may do so. Public comment is limited to five minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each board member and a copy (electronic preferred) for the official record.

The mission of the Nevada DUR Board is to work with the agency to improve medication utilization in patients covered by Medicaid. The primary goal of drug utilization review is to enhance and improve the quality of pharmaceutical care and patient outcomes by encouraging optimal drug use.

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair	Dave England, Pharm.D.
Netochi Adeolokun, Pharm.D., Vice Chair	Mohammad Khan, MD
Mark Canty, MD	Brian Le, DO
Crystal Castaneda, MD	Michael Owens, MD
Jessica Cate, Pharm.D.	Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2020

Date	Time	Location
July 23, 2020	1:00 PM	WebEx
October 22, 2020	1:00 PM	Hyatt Place, Reno, NV

Web References

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Drug Use Review Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/DUR_Bylaws_draft.pdf

Drug Use Review Board Meeting Material:

https://www.medicaid.nv.gov/providers/rx/dur/DURBoard.aspx

Social Security Act, 1927:

https://www.ssa.gov/OP_Home/ssact/title19/1927.htm

Meeting Minutes

DRUG USE REVIEW BOARD

Meeting Minutes

Date of Meeting: Thursday, April 30, 2020 at 1:00 PM

Name of Organization: The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).

Place of Meeting: Please use the teleconference/WebEx options provided below. If accommodations are requested, please advise using the information at the end of this agenda. Out of deference to Declaration of Emergency Directive 006 https://nvhealthresponse.nv.gov/wpcontent/uploads/2020/03/Declaration-of-Emergency-Directive-006-re-OML.3-21-20.pdf) from the State of Nevada Executive Department signed by Governor Sisolak as well as Emergency Directive 003 https://nvhealthresponse.nv.gov/wpcontent/uploads/2020/03/2020-03-20.Declaration-of-Emergency-Directive-003.pdf signed March 20, 2020, a physical location will not be open to the public for attendance at this time.

ATTENDEES

Board Members Present
Jennifer Wheeler, Pharm.D., Chair
Netochi Adeolokun, Pharm.D.
Mark Canty, MD
Dave England, Pharm.D.
Mohammad Khan, MD
Michael Owens, MD
Brian Le, DO
Jessica Cate, Pharm.D.

Board Members Absent
Jim Tran, Pharm.D.

DHCFP
Holly Long, Social Services Program Specialist
Beth Slamowitz, Pharm.D.
Homa Woodrum, Deputy Attorney General
Tammy Moffitt, Social Services Chief III, Pharmacy Services
Antonio Gudino, Social Services Program Specialist
DuAne Young, Deputy Administrator
Ellen Flowers, Program Officer
Lori Follett, Social Services Program Specialist

DXC
Jovanna Leid, Pharm.D.

OptumRx
Carl Jeffery, Pharm.D.
Daniel Medina

Managed Care Organizations
Thomas Beranek – Silver Summit Health Plan
Ryan Bitton – Health Plan of Nevada
Lisa Todd – Anthem

Public
Joe Ferroli, Takeda
Lisa Allen, Vertex
Ann Nelson, Vertex
Jimmy Lau
Brian Reeder, Ferrari Public Affairs
Janelle Hardisty, Novartis
Surbat Roychoudhary
Amy Rodenburg, Allergan
Deron Grothe, Teva Pharmaceuticals
Maria Agapova, Teva Pharmaceuticals
Ken Orr, Global Blood Therapeutics
Hector Mobine, Amgen
Debbie McDilda, Allergan
Karen Campbell, Amgen
Chris DeSimone, Akcea Therapeutics
Jenna Gianninoto, AbbVie
Brian McKenna, Tricida
Lori McDermott, Supernus
Josh Bishop
William Lai
Michele Lagerstedt, Vertex
Gregg Rasmussen, Vertex
Chi Kohlhoff, Viela Bio
Warner Quon, Ascendis
Brenda Nunnally, AstraZeneca
Mark Duerre
Nicole Robling
Jeana Colabianchi, Sunovion
Jon Glover
Crystal Henderson, Global Blood Therapeutics
Amanda Bustamante, Renown
Becky Gonzales
Sarah Day, RedHill Biopharma
Suzanne Hensley, Xeris
Tracy Mundt
Danika Webb, GBT
Mike Willett
Sharron Glass, Alimera Sciences
John Sekab, Akcea Therapeutics
Joseph Truong, University of Texas Southwestern Medical Center
Harleen Khaira, Envolve
Ben Droese, Amgen
Sarah Park
Ben Grossman, Novartis Oncology
Morton Hyson, Hyson Medical Products
Carmen Oliver
Hiten Patadia
David Riepe, Merck
Susan Leong, Envolve Pharmacy Solutions
Michael Zarob, Alkermes

AGENDA

1. Call to Order and Roll Call

Jennifer Wheeler: I am going to call the meeting to order. This is the Drug Use Review Board meeting. The time is 1:13. Welcome everybody. As Carl stated, we are going to have just a slightly different meeting, typically we would allow a little bit longer when we meet in public for public comment. So that is limited

to the three minutes as stated in the agenda. If I can please get a motion to approve the minutes from the January 23 meeting.

Mark Canty: So moved.

Homa Woodrum: Jennifer, this is Homa, you might want to start with the roll call first.

Jennifer Wheeler: Sorry. So, this is Jennifer Wheeler. I am a pharmacist in the state of Nevada.

Netochi Adeolokun: Netochi Adeolokun, pharmacist, Nevada, Reno.

Dave England: Dave England, pharmacist, Las Vegas.

Jessica Cate: Jessica Cate, pharmacist in Reno.

Mohammad Khan: Mohammed Khan psychiatrist, Las Vegas.

Mark Canty: Mark Canty family medicine Reno.

Holly Long: This is Holly. Is that all the members? Would you like us to go through the rest of this staff as well?

Jennifer Wheeler: The only one I didn't hear from was still Dr. Owens. I am sorry. I must have missed him. Mike, can you unmute?

Michael Owens: Michael Owens family physician, Reno, Nevada.

Jennifer Wheeler: And then yeah if everyone else can do an introduction as well please.

Holly Long: Carl, go ahead.

Carl Jeffery: This is Carl Jeffery. I am with OptumRx.

Holly Long: This is Holly Long with the DHCFP.

Homa Woodrum: Homa Woodrum, Deputy Attorney General for the State of Nevada.

Duane Young: Duane Young, Deputy Administrator, Nevada Medicaid.

Tammy Moffit: Tammy Moffit DHCFP.

Holly Long: Are we missing anyone for roll call?

Jovanna Leid: Jovanna Leid DXC Technology.

Holly Long: Did each of the MCOs speak? I am sorry if I missed that. I think I heard Ryan.

Ryan Bitton: You did, Ryan with HPN.

Holly Long: Tom and Lisa, can you introduce yourself?

Tom Beranek: Tom Beranek, SilverSummit. Can you hear me?

Holly Long: Yes. Thank you, Lisa? Lisa, I am not sure if you are trying to speak or not, but we are not able to hear you. You might need to log off and log back in and make sure your audio is connected.

Carl Jeffery: I unmuted her just now. Let me see, Lisa, are you there now.?

Holly Long: Lisa, are you there?

Carl Jeffery: She muted herself again. Now we can hear. There you go.

Holly Long: And then Jen, we need to allow for public comment and voting on the meeting minutes if we can just go through the agenda.

2. Public Comment on Any Matter on the Agenda

Jennifer Wheeler: Okay, perfect. So, we can open it up for public comment right now on any matter on the agenda.

Homa Woodrum: And this is Homa Woodrum, I want to acknowledge that I believe the members have all seen the written public comment that was submitted in advance of the meeting and they do have copies of that.

Lisa Allen: Hi. So, this is Lisa Allen from Vertex. Is this the point that you would want me to provide my public commentary or waiting until you get to the clinical presentations?

Jennifer Wheeler: If it is specific to something on the agenda, Lisa, then you could wait until we call for public comment for each thing on the agenda as well.

Lisa Allen: Thank you for clarifying. I will wait then.

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from January 23, 2020

Jennifer Wheeler: No problem. Anyone else for public comment at this time? Alright and then just really quick for our board members on Page 10 of the manual that went out if we could vote in that order. It is myself, then Netochi then Dr. Canty, Dr. Cate, Dr. England, Dr. Khan, Dr. Le, Dr. Owens, and then Dr. Tran would be the order. So, may I please get a motion to approve the minutes and anyone motioning, I think it would be easier to state your name and the motion. If that is possible, please.

Dave England: David England, move to accept minutes.

Netochi Adeolokun: Second.

Jennifer Wheeler: Thank you very much. Status update from Holly, please.

Homa Woodrum: Jennifer, you might want to have them vote on the meeting minutes approval. Thanks.

Jennifer Wheeler: Vote on the approval. Okay. Can we please vote on the approval of the minutes? Myself first, Jennifer Wheeler, aye.

Board: Ayes are unanimous.

b. Status Update by DHCFP

Jennifer Wheeler: Thank you very much. Holly go ahead with the status update.

Holly Long: This is Holly Long with DHCFP and Duane Young, our Deputy Administrator, will be providing the status update today.

Duane Young: Good afternoon, everyone. This is Duane Young Deputy Administrator for the Division. The last few months I understand, and I thank for everyone's patience today as we try to work through this meeting. This has become our new normal. So, you know, we appreciate everyone as we continue to work out the bugs being patient with us and understanding the level of time that staff are putting into this to make this meeting as transparent and as clear as possible. We also just want to acknowledge that staff have worked on many efforts regarding our response to COVID. There is a website. If you go to the DHCFP.nv.gov, and backslash COVID-19. You can find all kinds of helpful information of what the department is doing and how we are supporting providers and recipients alike during this crisis, including the changes that were made in pharmacy, as well as updates on our 1135 Waiver. We have also submitted a Disaster SPA. This is a very unique time for the Centers for Medicare and Medicaid (CMS) in that these SPAs are usually affected one or two states at a time or a certain region. There has never been a crisis in this modern era where all 50 states are impacted, and along with the territories, and so, CMS is having some challenges and they are going through those 1135 and the Disaster SPAs individually. They have provided technical assistance on multiple occasions to staff and so parts of the 1135 that were in the template have been approved. Other items that we requested are still pending. Staff have worked multiple times, even this week, with CMS and so those will be retro approvals. And so that will help to cover many of the things that you heard about in the Family First Coronavirus Act, such as covering testing for the uninsured. Those provisions are also being worked through with CMS through weekly calls and technical assistance. And so, the department is doing a lot and it's been meeting with all of its providers. I think the biggest influence, the biggest issue pharmacy has been getting is making sure that people have ways to get their medication and are being able to honor the stay at home order. And so, I will pause if there are any questions, I guess first from the board in regards to this report. Alright, hearing no questions. I will then yield the floor to Chairwoman Wheeler.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for calcitonin gene-related peptide (CGRP) receptor inhibitors.

Jennifer Wheeler: Thank you so much. Carl, would you like to start with the clinical presentations, please?

Carl Jeffery: Yes, thank you. Do you want to open it for public comment?

Jennifer Wheeler: Yes. So, the first medication the CGRP inhibitors. There is three of them in here, Ubrelvy, Aimovig and Emgality. Does anyone have any public comment? We will start with the first one Ubrelvy.

Josh Bishop: I am sorry. I was on mute. This is Josh Bishop with Allergan; I do have a public comment for Ubrelvy. I apologize.

Jennifer Wheeler: Go ahead, Josh. Thank you.

Josh Bishop: So, as I said, my name is Josh Bishop. I'm a pharmacist in the R&D Department at Allegan. I'm here to talk about ubrogepant which has the brand name of Ubrelvy. Ubrelvy was approved in December for the treatment of migraine with or without aura in adult patients. It is an oral CGRP receptor antagonist. And as you probably know, CGRP is one of the primary neuropeptides that are known to cause the pathogenesis of migraine. Blood and saliva levels of CGRP are elevated during a migraine attack. And we know that blocking CGRP signaling, as ubrogepant does can reduce vasodilation and reduce nociception. Importantly, this mechanism has not been associated with vasoconstriction like the triptans, has been proven to be safe in patients with cardiovascular disease. Ubrogepant is an orally administered tablet and it's available in 50 and 100 milligram doses. The recommended dose is 50 or 100 milligrams as needed. A second dose may be administered two hours after the initial dose. The maximum dose in 24 hours is 200 milligrams. In a 52-week long-term safety study, ubrogepant was studied for the treatment of up to eight migraines, with up to two doses per attack every 30 days. Clinical trials efficacy was measured by the co-primary endpoints of pain freedom, and the absence of the most bothersome symptom at two hours. Both 50 and 100 milligrams show statistically significant response in both endpoints after a single dose. Approximately 60% had pain relief at two hours, 20% were completely pain free, and approximately 38% had full resolution of their most bothersome symptoms. Those that needed to take the second dose, greater efficacy and pain freedom was seen after the second dose with up to 55% of patients who took that second dose, achieving complete pain freedom. The most common adverse events, as listed in the PI are nausea and somnolence. And those rates are similar to placebo. Ubrogepant has only one contraindication, which is related to the concomitant use with strong CYP-3A4 inhibitors. It has no warnings and precautions, including no cardiovascular or medication overuse headache warnings. We are pleased to have brought this first non-serotonergic agent and first truly novel mechanism of action to the acute migraine market in the last 30 years. Additionally, the safety of ubrogepant has been established and is not a controlled substance, as with other newly approved acute migraine agents. So, in summary, ubrogepant is a first line agent that has three main advantages. First, data so far suggest that ubrogepant does not cause medication overuse headache, as many of the current treatment options do. Second, ubrogepant can be used in patients with cardiovascular disease, or those patients who have multiple risk factors associated with cardiovascular disease, who cannot take a triptan or an NSAID due to their labeled contraindications, warnings and precautions. And lastly, ubrogepant is the only acute migraine product that has established second dose advocacy for patients whose symptoms are not well

controlled after a single dose. In conclusion, Allegan respectfully asks for access and those patients with cardiovascular risks and those who are unresponsive, who cannot tolerate triptans. Thank you.

Jennifer Wheeler: Thank you very much. Carl, do you want to go through this, or do you want to do one drug at a time? Or do you want me to open it up for each drug and then present them?

Carl Jeffery: I think it would be better just open it up for the whole class. I know there was somebody for Ajovy as well.

Maria Agapova: Hello. This is Maria Agapova for the Ajovy. Thank you to the committee for the opportunity to address them today. My name is Maria Agapova, I'm a Senior Medical Outcomes Liaison and representing Teva Pharmaceuticals. I'm here to provide information about Ajovy, fremanezumab. Thank you for updating the monograph for the latest focus trial data. Most of the large body of content in the testimony has always already been reviewed. So, I will focus on three main points and start with the last bullet on the page and update my own information. As of Monday, April 27, Ajovy auto injector became available, making Ajovy the only long acting anti-CGRP with the option of dosing at home or in the provider's office as few as four times per year either with the auto injector or prefilled syringe. So, as you see, there are many options for patients to find the right regimen for themselves. The next point I would like to make is an update on the long-term data in the 12-plus months of treatment with Ajovy. Clinical trial open label on safe or long-term safety Ajovy, there were very few withdrawals due to adverse events roughly 4% and low incidence of cardiovascular and cerebrovascular events, no signals of liver toxicity, anaphylaxis or severe hypersensitivity were detected. And then lastly, speaking to acute medication overuse of post-hoc analysis of the pivotal trial, chronic migraine population, reductions and overuse are observed in patients treated with Ajovy. And as an update reversion out of medication overuse status measured through month 12 roughly 60% of patients with acute medication overuse at baseline. Based on these findings, I asked the committee to consider allowing access to preventive CGRP inhibitors to patients who may be overusing acute medication. Thank you. I yield the remainder of my time to the committee or to address any questions.

Jennifer Wheeler: Thank you very much. Anyone else for Aimovig or Emgality? Carl, do you want to begin with a clinical presentation?

Carl Jeffery: Yes, I will. So, we have kind of a different idea for the formats here, let me blow this up a little bit bigger. So, we heard about the CGRPs that I was going to provide a quick overview, but I think everything that I was going to say has been said. I'm not going to rehash what has already been said. I do want to point out to the board that there are two new agents that have been recently approved, so we will likely see this class again, there's a new Vyepti is a new IV formulation. It is dosed every three months for the prevention of episodic and chronic migraine. And then there is another for acute treatment and this Nurtec, rimegepant is an ODT dose for acute treatment for migraines, with or without, aura in adults. Again, these I think we will be seeing these in the near future. But today, we are going to be talking about the Ubrelvy, the new one that is in this class. We heard the overview already, about the two studies. It has got an indication for the acute treatment of migraine with or without aura in adults, two studies did show it is better than placebo. I am going to show the utilization really quick on this one. When we looked at the utilization on the CGRPs we do not see Ubrelvy here. It was not actually introduced, it was not on the market, until I think it was late last year, so it didn't have any utilization yet. We can see how the products are going here. We do have, we have taken this class to the Silver State Scripts Board, and they have made Emgality non preferred the Aimovig and the Ajovy are the two preferred products. Aimovig certainly has the bulk of the market share. Ajovy fluctuations could be due because this can be dosed every three months. So that could be why we do not see the number of claims as some of the other ones.

I have the proposed criteria and what we are doing a little bit differently is presenting it in the format that is commonly seen in Chapter 1200. And I think this will help the board see what all the changes are that we are proposing. It is a red line down here so we can see what updates we are making. And it mirrors the information in the binder, so that there's a couple changes. I just want to point out to the board, the top page up here is just the triptans and no changes are being made to the triptans since they're not agendized, either, so these are the CGRP. The big changes we have them currently the criteria has essentially a trial of three different product classes. So, we have to try all three of these prior, the antidepressants, and a product like Depakote or Topamax and a beta blocker. And where we would like to see that is to go to at least two of the three classes. The wording has been updated to show that you just have to try two of the other classes and that is reflected in the chronic migraines as well here. Emgality has a new indication for episodic cluster headaches. And so, like what is in that binder is the criteria here is the initial request would be recipient has a documented diagnosis of episodic cluster headache. The recipient has experienced two cluster periods lasting from seven to 365 days separated by pain free periods lasting at least three months. The recipient must be 18 years of age or older, prescribed by or in consultation with a neurologist or pain specialist. For the new product Ubrelvy the criteria for the acute migraine would be the initial request the recipient has a diagnosis of acute migraine with or without aura, the recipient must be 18 years of age or older, the prescribed dose will not exceed two doses per migraine episode, and treating no more than eight migraine episodes per 30 days and prescribed by or in consultation with a neurologist or pain specialist. That summarizes the proposed criteria changes we have here I'm open for any feedback from the board.

Netochi Adeolokun: Hi, Carl, this is Netochi. I had a question in regard to the Ubrelvy. Do patients need to try a triptan or something first, prior to Ubrelvy?

Carl Jeffery: We do not have that as a step requirement. I mean, that is something we could certainly require that they have tried something, I think that is prudent.

Netochi Adeolokun: Thank you.

Jennifer Wheeler: This is Jen. I agree with adding that criteria for the Ubrelvy, maybe trial and fail of one triptan. Holly, have you seen anything else from any of the other Medicaid's that alluded to trial and fail of one to two different triptans?

Holly Long: I did not see that specifically. I would have to look into that for you.

Jennifer Wheeler: Oh, no problem. So, any feedback from any of the other board members and considering adding that to the approval criteria?

Dave England: This is David England, as I was looking at the information that Carl was sending us, in my mind, I am used to seeing more like an algorithm. We go from here to here to here to here. And as long as we are starting out with them, the more standard therapies, as those that work, we go to the triptans, those do not work, then we go to the CGRPs. I can kind of follow that line. I do not see it as a straight line here. But it makes sense to go, you know, to go through this standard, a standard process and the algorithm, rather than just jump to individual agents, or classes.

Carl Jeffery: Dr. Wheeler, sorry to interrupt, I am getting a message that there was a provider on the line who is trying to give testimony but cannot unmute. Can we go back to go back this provider to give some testimony?

Jennifer Wheeler: Yes.

Carl Jeffery: I guess they have just phoned in. So, I am going to unmute some of these phone lines here and see if we can find this provider here.

Jennifer Wheeler: Homa, is there anything that I need to do differently? I opened back up to public comment after we have done the presentation or Is that okay?

Homa Woodrum: It is fine to take the comment just remind the members that you are not engaging specifically with a public commenter, so they may say something in relation to the discussion you have had just now. But you can just take that under advisement, you are not engaging with them. So, that is fine to take the comment.

Jennifer Wheeler: Okay, perfect, Carl, if you can get their audio setup. We will be more than happy to listen to what they have to say.

Carl Jeffery: I think it's Dr. Heissen.

Dr. Heissen: Hello.

Carl Jeffery: Oh good. We can hear you go ahead.

Dr. Heissen: Oh good. Thank you. I am a neurologist and I am speaking briefly about Ubrelvy. It has been working great for my patients. I have been looking for years for a medication other than a triptan to take the abortion of migraines that is not addicting. We have an opioid crisis as you know and so many of the medications that we use for migraines are addictive such as Fioricet and Tylenol With Codeine and Norco and hydrocodone, it goes on and on and on. They cause rebound headaches. They cause more headaches and long term and it causes addiction. Ubrelvy works very well, it doesn't have the side effect profile of the triptans. I have patients who actually told me it is miraculous. So far, every patient I have tried it on has helped, I hope we can get it first line, and then I hope it can be approved by Medicaid and all the insurance companies. It has been very, very effective. And it is a population that really needs new treatments. There are literally millions of patients in this country who have suffered from migraines and tension headaches and this would be a very useful addition to the armamentarium. That is it in a nutshell. It is very, very effective medication and has a very safe side effect profile.

Jennifer Wheeler: Thank you so much. Any other board members have any comments regarding the addition of what we had discussed with step therapy? In favor or not.

Carl Jeffery: Okay, so one of the advantages we have with this process I can update it live here. I have made the update. Is this kind of language, we tried and failed at least one triptan product? Any other comments from the board or updates or is this it?

Jennifer Wheeler: I think that looks good, Carl. Alright. Okay, so if I could please get a motion to approve the presented criteria, just with the addition of line C under acute migraine. The member has tried and failed at least one triptan product.

Dave England: David in Las Vegas, so moved.

Jennifer Wheeler: Can I get a second please?

Mark Canty: Mark Canty, second.

Jennifer Wheeler: Thank you all those in favor, aye. Jennifer Wheeler.

Board: Ayes are unanimous.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for cystic fibrosis agents.

Jennifer Wheeler: Thank you very much. We will move down the line. Next up is going to be the cystic fibrosis medication on Page 57, Trikafta. If I can open that up for public comments.

Lisa Allen: Hi, this is Lisa Allen from Vertex. Good afternoon. Thank you very much for the opportunity to provide testimony on behalf of the CFTR-modulators for the treatment of indicated patients with cystic fibrosis. As I said, my name is Lisa Allen, I am with Medical Affairs at Vertex pharmaceuticals. I would like to begin by reminding the board that there are currently four FDA approved CFTR-modulators from the Vertex portfolio and Trikafta or elexacaftor, tezacaftor and ivacaftor is the most recently approved modulator and it is indicated for patients with CF 12 years of age and older who have at least one F508del mutation in the CFTR gene. Approximately 17,300 us patients with CF are now eligible for Trikafta. Approximately 5,900 of those patients Trikafta will be their first and only indicated CFTR-modulator therapy. And then an estimated 6,800 US patients that are currently eligible for Kalydeco, Orkambi and Symdeko are not eligible for Trikafta based on genotype and or age. Kalydeco is indicated for the treatment of CF in patients six months and older, who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and or in-vitro assay data. Symdeko is indicated for the treatment of patients with CF six years of age and older, homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that's responsive to tezacaftor/ivacaftor. Orkambi is indicated for the treatment of CF in patients two years of age and older, are homozygous for the F508del mutation. All four of these CFTR-modulators are systemic therapies that work by targeting the underlying cause of cystic fibrosis, which is the defect in the CFTR protein. Importantly, CF is a multi-organ disease. And the objectives of care include preserving lung health, optimizing nutritional status, overall improvement of respiratory manifestations, including pulmonary exacerbations and other outcomes. Clinical studies with Vertex CFTR-modulators have shown positive impact on multiple clinically important outcomes in line with these treatment objectives, including lung function as measured by percent predicted FEV1 pulmonary exacerbations, nutritional status as measured by BMI and patient-reported outcomes from the CFTR respiratory domain. The complete list of warnings and precautions associated with Trikafta, Kalydeco, Symdeko and Orkambi can be found in each product respective us prescribing information. With that background, I would like to specifically address the draft policy for Trikafta that was proposed by SilverSummit Health Plan. Vertex is extremely concerned with several proposed criteria that are not based on scientific or clinical evidence. As proposed, the SilverSummit Health Plan policy restricts all eligible members with CF from having any access to Trikafta. The rationale for Vertex's concerns regarding the proposed arbitrary restrictive criteria have been communicated to the board prior to this meeting. With that said Vertex strongly agrees with the coverage and limitations policies for the CFTR-modulators, proposed by OptumRx on January 2. I am here to encourage the board to officially adopt these policies.

Holly Long: Thank you so much. I have to interrupt you there you have been on for over three minutes. If you can go ahead and wrap it up, we will have to move along and provide other people time for public comment.

Lisa Allen: Okay, thank you. I would just like to close by saying that we are committed to the CF community. And we share a sense of urgency for people with CF, their caregivers and clinicians. And for these reasons, I respectfully request the board to adopt the preauthorization and recertification request criteria, as initially proposed by OptumRx. Thank you. And I would be happy to answer any questions.

Holly Long: Carl, I am going to stop you right there. This is Holly Long, sorry, I apologize. We are all getting used to this process. And we are a little bit challenged, but we are trying to make sure that we address everything correctly. And I want to back up a little bit if we can on the agenda, and I believe that the first item that was agendized. We did not give the MCOs time to present any other criteria or speak to anything. If we can back up to Ubrelvy and just see if there's anything that any of the MCOs need to speak to before we move along. Sorry about that. And I do not know if Lisa's audio is working or not, I was unable to get ahold of her. If she does not get on, nope, there she is, great.

Lisa Todd: Yeah, I broke the rules. And I hung up and then just called in by my phone. So, I am sorry, my name will not appear by my phone number. I could not get audio to work connecting the other way. I can hear you guys fine, but you guys could not hear me.

Carl Jeffery: Yes. It is actually working just fine. It has your name there. So, you can go ahead.

Lisa Todd: Oh, good. Okay, so with that, did you, were we wanting to go through and talk about our criteria?

Carl Jeffery: Yeah, I think you have an opportunity, I think we have read through and approved the proposed criteria. But if there is anything that you want to speak to or make updates to.

Holly Long: Just if there is anything you want to speak to that is different. Lisa, you do not have to speak to anything. It is totally up to you. However, if anything, any of the information that is provided by you, or Ryan or Tom from any of the MCOs would cause someone to change their vote, then Jennifer, Dr. Wheeler would need to ask for a motion to reopen the discussion due to the MCOs comments, just in case. But otherwise, it is up to you if there is anything you want to share on Ubrelvy.

Lisa Todd: Okay, so that was the first drug that we did, though. I just have what I had in the form. So, I do not know if you guys want me to talk about what I put in the form, it was just maybe some additional criteria you might want to consider. I don't think it is absolutely crucial either. So, do you want me to go through that that I put on the form?

Holly Long: It is totally up to you, Lisa. And I, we can all see it right now. So, if anyone wants to speak to it and say that they would like us to go over anything, that is fine. Um, you know, if there is anything different than what was proposed that you feel like you would like to speak to for Anthem, I think that that would be appropriate. Otherwise, we can just move through Ryan and Tom and move along.

Lisa Todd: I do not have anything to add other than what was on my form so I am fine. Thank you.

Ryan Bitton: This is Ryan with HPN, we were on board with what was presented and completely on board with triptan failure first. We prefer probably more than one triptan. As you can see what I had built, but definitely having the other prophylactic therapies, one of each of those things is appropriate. So that is all HPN had to say.

Tom Beranek: And for SilverSummit, we were good with the proposed criteria. I did not put anything for that drug, anything additional.

Jennifer Wheeler: Thank you, guys. Okay, Carl, if you want to swing back through for the presentation for Trikafta, please.

Shipra Singh: Hi, sorry to interrupt. This is Shipra and I am one of the pediatric pulmonologists. Is the public comment done for Trikafta or are we still because we were kind of going back and forth? I was not sure when to talk about it.

Jennifer Wheeler: Nope. If you would like to go ahead and start, we will give you three minutes.

Shipra Singh: That sounds great. And as I said, I am Shipra Singh. I am the Co-Director of the CF Center, here at Renown Health in Reno, and I am a pediatric pulmonologist and I just wanted to comment on some of the criteria proposed by the SilverSummit Healthplan. Specifically, in regards to the FEV1 criteria that is proposed. I do think and when I say I, I am speaking collectively for the CF community here in Reno and hopefully as the foundation as well that these criteria are very restrictive and I think they will prevent some of the very severe patients from getting the benefits of the Trikafta. Some of the testing, as what is proposed with the chloride transport is not something that we do clinically on a daily basis. So that would make the validation of the drug very restrictive. Especially since we do not do this. The other thing that I wanted to talk about was the duration of approvals, duration of four months, typically we like to see anywhere from six to 12 months just for the ease of the paperwork. And so, if those can be considered by the board during this meeting, I would appreciate that. Thank you.

Jennifer Wheeler: Thank you very much. Does anyone else have any public comment at this time?

Carl Jeffery: If people are still trying to talk, we can go through the letters. We received several communications from the community about Trikafta. The board was provided copies of all of this information and this will be posted shortly after the meeting. I will go through these real quick just to show which ones were requested we got; this is from the Executive Director of the Cystic Fibrosis Research Incorporated. And then there is a letter from Vertex and other Cystic Fibrosis Foundation. Other ones, there is another one here from the children's lung specialist. And again, the board has all of these, the Vertex response here was directly addressing some of the criteria that SilverSummit had proposed.

Holly Long: This is Holly Long. If I could just add to that as well, not only is Carl going to be presenting each of the documents that were provided for public comment, if any of those were provided to us, they will also be posted as attachments on the DHCFP public notices site, I am usually able to get them posted within 24 hours, does not mean there are not any IT issues. So, if anybody needs access to those should be up as an attachment with this meeting posted on those public notices as well. Thank you.

Carl Jeffery: Okay, I do not know if there's any other public comment, but I can move forward here.

Jennifer Wheeler: Yeah, go ahead, Carl. If someone presents with public comment, we can go back to it.

Carl Jeffery: Okay. So, let me show the utilization real quick.

Brian Le: Can I ask you a question?

Carl Jeffery: Yes.

Brian Le: This is Brian, did you hear me? Because Holly text me that they do not see me on the phone. You cannot see me.

Carl Jeffery: I can hear you. And as long as you can see your screen that is all that matters. I think we are all set then.

Brian Le: Okay.

Carl Jeffery: Okay, so that's good we have Dr. Le, so it is good. So, the information here, we heard a good overview and again, they stole my thunder. I wrote up a nice presentation about how we are talking about the new Trikafta, the different products, and we heard all about how it is the F508del mutation, and this new Trikafta is expected to treat about 90% of the people with this copy here. I think there is some good advancement and with this one, we heard about the two published trials showing that it is effective. They have had an active competitor. Looking at the utilization here, Trikafta was introduced in October of 2019. And if you look at the last two months, and this is just through December, you can see already the last, even the last two months when it was available in this year, you are already seeing it, a pretty good number of claims for this medication already. Since then, it is not reported here, but we have seen it continue to go up, so I think it is a very favorable medication and providers certainly like it. Our proposed criteria and we will go through the OptumRx criteria first. One of the first things you will notice here is that we have combined all of the cystic fibrosis agents into a single criterion. Before, the Kalydeco, Orkambi and Symdeko had their own independent criteria. Nothing is changed, it is just all combined into a single document. So, Kalydeco, Orkambi and Symdeko are the same one, but for OptumRx's proposed criteria the Trikafta is proposed over here. We have that the recipient has a diagnosis of cystic fibrosis, the recipient is 12 years of age or older. The recipient has at least one F508del mutation of the CFTR gene and the medication is prescribed by or in consultation with a pulmonologist or specialist affiliated with the cystic fibrosis care center. That was it for the presentation for the OptumRx criteria, we can go through the other plans, the MCO's.

Jennifer Wheeler: Okay, do you have Anthem up there?

Carl Jeffery: Yeah, I am getting it pulled up here.

Lisa Todd: The only thing that I had on my criteria is that it was just an addition if the board wanted to consider it, we have in there. But we agree with everything that Optum has, this would just be additional information if you wanted to include it. On my form, it talks about mutation testing confirms the individual has two copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene. And then also we did have like disqualifying criteria that we do look to make sure that the member is not on those other meds that are similar to that or that the member does not have severe hepatic impairment.

Carl Jeffery: Did you want to speak to the utilization?

Lisa Todd: We have only had two members receive this medication, the Trikafta so, no nothing. We do not have a lot of people on this.

Ryan Bitton: Thanks Carl. This is Ryan from HPN, we approve what you have presented for Trikafta, utilization is fairly boring. I suppose I am a little out there too. No Trikafta yet.

Tom Beranek: I have gotten quite a bit of feedback from Vertex both locally and the corporate level regarding what I submitted here. As everyone on the committee knows we submit these a couple months

before the meeting to make sure we give plenty of time for folks to read down and things of that nature and our clinical corporate team has reviewed this. Our clinical policy team has reviewed this policy, again, since I made these recommendations. So, I have got the six bullet points here. The first one we want to keep I will go into that here in a second, chart notes indicated pulmonary function tests performed in the last 90 days show forced expiratory volume is between 40 and 90%. Next one, in-vitro testing, and baseline chloride transport, we have removed that from our policy. So, I'm no longer recommending that be included. Third one, Trikafta is not prescribed with other CFTR-modulators, we are recommending that remain fourth one, again, the chloride transport one, we had removed that from our policy as well. And then the last two dose and approval I always put those again. Sometimes we do and sometimes we do not have approval duration of four months. That is just what our corporate policy is not real hard and fast on that one. I know sometimes the group here decides longer or shorter depending on sort of what everybody agrees upon. Speaking to specifically the first one, chart notes indicate pulmonary function tests performed within the last 90 days, percent to FEV1 that is between 40 and 90%. So, based on feedback I have gotten from our clinical team, according to the Cystic Fibrosis Foundation lung transplant referral guidelines published in 2019. The best evidence-based option for these patients is to discuss potential of lung transportation rather than drug therapy. The foundation recommends, especially on transportation with all individuals with an FEV1 of less than 50%. For individuals with cystic fibrosis 18 years of age and older, the foundation recommends lung transplant referral no later than when I have got three things here. FEV1 is less than 50% of predicted and rapidly declining. Then [inaudible] 20% relative decline within 12 months. [Inaudible] FEV1 is less than 40% predicted markers of short-term survival. The third FEV1 is less than 30% predicted. That is for those that are 18 years of age and older. For those 18 years younger, one, FEV1 of less than 50% of predicted and rapidly declining, and that is the greatest decline in 12 months. Second one is FEV1 of less than 50% with markers of short survival, and lastly, FEV1 of 40 percent predicted. So that is SilverSummit HealthPlan's comments on this policy of what we are recommending. Thank you.

Jennifer Wheeler: Thank you, Tom. Do any of the board members have any criteria that they would like to add or review in addition to what Carl has presented based off the other MCO recommendations?

Dave England: This is David England. I have a hard time reading some of this print on my end, even on my big screen here. But the OptumRx recommendations also include or conclude that it would not use more than one product at a time. I did like this comment from Anthem and SilverSummit that they cannot be concurrently on other CFTR-modification agent. Otherwise, the criteria looks good to me. Yeah.

Carl Jeffery: Yeah, we do not have any criterion here that says that you are only on one at a time. I think this would be worthwhile adding maybe it is an overarching criterion before we get to any of them.

Dave England: I did not hear anything with comments that said that you would need to be on more than one of these. I kind of get the impression from the comments and also from the criteria you presented, that some people are going to work well, for some people what is going to work well for another one. So, yes, have all four available, but I do not get any impression that all of them concurrently but would do any better. So I like the idea of one or the other, but I do not think we need to restrict you do not have to go through a pecking order so to speak is pretty much what works, works, but we do not need to have two on board at once.

Carl Jeffery: The Kalydeco is ivacaftor the Orkambi has ivacaftor in there with lumacaftor. Symdeko has ivacaftor plus tezacaftor. So, they are similar agents. They just have a different combination of them. I actually think that being used in combination with one another is pretty rare. I think if it did happen, I am

not sure it would be intentional, we can just to safeguard that I think that rule in there to say only one at a time.

Jennifer Wheeler: Any other board members have any comment? Carl in the past with some of these medications we have been able to offer kind of like a soft DUR just to warn about because of the effects on the liver. The CYP-inhibitors for like Clarithromycin, is there a possibility? I know it doesn't have to do with this portion but...

Carl Jeffery: Yes, that would be something identified through the DUR, the ProDUR edits. So, yeah those would certainly be identified as any drug-drug interaction

Jennifer Wheeler: Perfect.

Carl Jeffery: Alright, so I just added up here and I do not know if this language is good enough we could certainly tweak it a little bit as needed, but I just put it in there kind of overall, above everything else approval will be for a single agent will be given if the following criteria are met and documented. And it goes down to that the new criteria for the Trikafta.

Dave England: That looks good to me.

Jennifer Wheeler: Homa, will I have to call for two separate motions then to approve, one to alter where we went as a class to change it to no duplicate agents and then a second one for the Trikafta criteria as-is?

Homa Woodrum: This is Homa, I think it just depends on how somebody wants to make the motion. If they tend to like both and you can do them both at once or you can separate them out. I think it is just a matter of preference.

Jennifer Wheeler: Okay. I will call for a motion to approve both at the same time the addition to the overall class, adding no more than one agent and then motion for accepting Trikafta as presented.

Dave England: This is Dave England, so moved.

Mark Canty: Mark Canty, second.

Jennifer Wheeler: Thank you very much. If we can vote now, all those in favor, say Aye.

Board: Ayes are unanimous.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for narcolepsy agents.

Jennifer Wheeler: Alright. So, next we will move to open for public comment on Wakix, the narcolepsy medication. Anybody here representing?

Carl Jeffery: I am not seeing anything, and all the other phone lines are un-muted, nobody is raising their hand.

Jennifer Wheeler: Alright Carl, do you want to go ahead with the clinical presentation please?

Carl Jeffery: The narcolepsy agents here we have the new agent Wakix or pitolisant. This medication is indicated for the treatment of excessive daytime sleepiness in adults with narcolepsy. This is an H3 antagonist or inverse agonist. It shows no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy. The safety and efficacy was evaluated in two eight-week active controlled trials and they are a little underwhelming. The harmony one was Wakix versus modafinil with 94 patients. It was shown to be superior to placebo but not non-inferior to modafinil, so there is a lot of negatives in there and same second follow up harmony trial compared to modafinil at 166 patients. Again, shown superior to placebo but not non-inferior to modafinil. When we get into the utilization of this class, we do not see any claims for the Wakix. It was introduced, at least it was added to their drug file in September of 2019. We do not have any claims for it. Our proposed criteria is pretty straightforward with this one we included it with the other ones. This will be included with the rest of the narcolepsy agents in this class here. So, we have got that Provigil, Nuvigil and now include the Wakix and then Xyrem. So, the criteria would include the approval will be given if the following criteria are met and documented, Wakix, pitolisant, the recipient has a diagnosis of narcolepsy with excessive daytime sleepiness. And it is about as easy as it gets with that one. And based on the studies, I am not sure how much use this one is going to get, but I think there is probably a market for it for maybe having a non-stimulant or non-controlled option for some of our high-risk patients.

Jennifer Wheeler: Thank you, Carl, do you want to bring up I guess we will do Anthem first, just to be consistent with the order.

Lisa Todd: Hi, yes, this is Lisa Todd from Anthem. We agree with the proposed criteria. The only thing is that we had an additional criteria to consider for approval is that if a member has the cerebrospinal fluid hypocretin-1 deficiency and then we have more disqualifying criteria, the severe hepatic impairment or risk factor or for prolonged QT interval or the member is using another drug that increases the QT interval. But, like I said, we approve the OptumRx criteria. And then as far as utilization we don't have any utilization any claims on this new drug either. Thank you.

Jennifer Wheeler: Thank you, Lisa. Ryan HPN?

Ryan Bitton: Yeah, just a couple of additional things. In our criteria, we recommended the confirmation of narcolepsy via a sleep study and symptoms of daytime sleepiness as listed there and then failure of other products already in the market. That's two generics, generic like Nuvigil and then an amphetamine or methylphenidate. And then Sunosi, that's another product on the market or having a contraindication due to substance abuse disorder. So, those are the recommendations about previous use of some other things around qualifying the diagnosis. As far as the utilization goes, you can see that there is a lot of utilization to the two generics of Provigil and Nuvigil and not much for, or nothing for the new drug, very little for Sunosi as well.

Jennifer Wheeler: Thank you, Ryan. Tom SilverSummit.

Tom Beranek: Yes, we made a couple of recommendations, prescribed by or in consultation with a neurologist. I have age restriction greater than or equal to 18 years of age and then similar to what I am proposing in terms of, we had a timeframe here but failure of one month trial of generics of Nuvigil or Provigil, maximally indicated doses and then put in a dose recommendation not to exceed 35.6 milligram or two tablets per day. And then our usage, really not a lot of use for any of them, and six was the most we had back in March 2019. Since then, it has been four or under so not a lot to talk about here. Thank you.

Jennifer Wheeler: Thank you, Tom. Any comments from the board on addition of any additional criteria presented by the MCO? The only thing I would like to consider perhaps is in agreement with SilverSummit and adding the 18 and older. I pulled the package insert and it lists the studies that was only studied in adults 18 and older so I'm not sure that is something we'd like to consider. Thank you, any comments from the board on agreeing or disagreeing with that recommendation?

Brian Le: This is Brian Le, I agree with that recommendation. I also have a question on this because Lisa brought up the QT prolongation. So, should we put some restriction on them as well as on the patient on the end stage renal disease? Because that is what it is not supposed to be for them either. So, should we put a little bit more restriction or clarification about those?

Carl Jeffery: We certainly can. I think there is always a discussion about like, how much should our policy dictate what the prescribers should be doing and do their due diligence. Some of this is just the practice of medicine and between the prescriber and the pharmacy. They should have this already set. Some of this could be repetitive but it certainly adds a little burden to provide that information when it is already been done, but they just have to document it and send it in. So, then certainly I am open to entering information into the criteria.

Dave England: This is David England, I would like to add 18-year old criteria. I am kind of neutral on the QT prolongation, it has gotten to the point where what does not prolong the QT interval anymore, so I am kind neutral on that, but I definitely like the added 18 years of age on it.

Jennifer Wheeler: I am kind of with Dr. England on the sense that the 18 and older I agree with, but I am not sure about the QT. Carl that would still pop up, you know, with the drug-drug. Right?

Carl Jeffery: It would be drug interaction that would, yeah, that would show up. And then if there were, you know, it wouldn't necessarily catch it if they just have like some other medical condition or something. Sometimes it can get that from an inferred diagnosis.

Jennifer Wheeler: Any other comment from any other board members? Alright. So, if I can ask for a motion to approve the criteria as presented with the addition of the recipient must be 18 years of age or older.

Netochi Adeolokun: This is Netochi, I will motion.

Michael Owens: This is Mike Owens, I second that.

Board: Ayes are unanimous.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for sickle cell anemia agents.

Jennifer Wheeler: Thank you very much. Moving on to the next medication the Oxbryta. The sickle cell anemia agent. Does anybody have public comment? Now is your chance.

Jennifer Nelson: Hi, this is Jennifer Nelson from Global Blood Therapy. I am a Medical Science Liaison with Global Blood Therapeutics. Thank you for the opportunity to speak with you today about Oxbryta or voxelotor tablet, a first in class hemoglobin-S polymerization inhibitor, indicated for the treatment of sickle cell disease in adults and in patients 12 years of age and older. This indication is approved under an

accelerated basis with the FDA based on the increase in hemoglobin and continued approval is based on the assumption of clinical benefit and confirmatory trial. As many of you know, patients with sickle cell disease have very few treatment options for this devastating condition. Oxbryta has a novel mechanism of action addressing, you know like anemia caused by sickle cell disease. It is a once-daily medication has a rapid onset of efficacy in as little as two weeks and does not require extensive monitoring or titration in those patients, and data to date has shown it as well tolerated. Global Blood Therapeutics supports a safe and appropriate use of Oxbryta. I would like to review some of the recertification criteria that we will send in for public comments, I just wanted to highlight a few things. The current criteria are documentation of positive clinical response to arthritis. Examples are increases of hemoglobin of greater than or equal to one gram per deciliter baseline and decrease annualized incidence rate of VOC. The second criteria is documentation of the recipient's hemoglobin level does not exceed hemoglobin of 10.5 grams per deciliter. In reviewing the documentation, and examples of time to clinical response, with Oxbryta there is documentation in the health study that patients did respond with rising hemoglobin less than one gram, but with a positive clinical response, and I just like to touch on some of the examples that were sent in for written comments. With a post-hoc analysis of the head study that showed measures of hemolysis that will reduced in patients that had a hemoglobin radicals less than one gram per deciliter. Specifically, the market does analysis, and secondary endpoints were indirect bilirubin that was reduced by 29% and mean reduction in their percent reticulocyte count of roughly 20%. With regard to the second criteria, that the hemoglobin must not rise above 10.5 grams per deciliter, while the hope study had boundaries for study inclusion of hemoglobin 5.5 to 10.5. The actual hemoglobin rise in the study was up to 13 grams per deciliter. The range between seven to 13 grams per deciliter. And so, perspectives and normal range of hemoglobin levels, it's in 12 to 17.5 grams per deciliter. Also, a post-hoc analysis of the hope study showed that patients that achieved the greatest absolute hemoglobin level had the lowest incidence of VOC. This revealed that higher levels of hemoglobin did not translate into increased risk of VOC suggesting that viscosity is not increased with Oxbryta treatment.

Holly Long: Thank you. That's in your three minutes. So, if you could go ahead and wrap it up, I appreciate it.

Jennifer Nelson: Thank you. And as it goes to show, improvements in both sickle cell disease complications and markers of hemolysis have been used to indicate Oxbryta' s efficacy, other than the primary endpoint of greater than one gram per deciliter. I appreciate your consideration of these criteria. And I am open to any questions that you may have.

Jennifer Wheeler: Thank you very much. Anyone else for public comment at this time?

Janelle Hardisty: Yes, would like to address the committee about Adakveo. This is Janelle Hardisty, I am a Hematology Oncology Outcomes Liaison for Novartis Medical Affairs. And I am joining you today to speak about crizanlizumab or Adakveo. This is a medication for reduction of vaso-occlusive crisis or VOC in Sickle Cell patients who are 16 years or older. And I would like to just share three key points with the committee as you consider this for Nevada Medicaid patient access. The first point is unmet need. Sickle cell disease is really a global health problem. And with us in the United States, sickle cell disease patients die on average about 20-30 years before patients without sickle cell disease. And although a handful of medications are FDA approved to treat sickle cell disease. Treatment limitations exists based on both patient perception of efficacy, safety and low adherence in the instance of hydroxyurea, as well as social stigma in the case of opioids for treatment of pain. Vaso-occlusive crises are the hallmark of sickle cell disease and vaso-occlusive crises lead to severe pain, decreased patient quality of life and can cause life threatening complications. They are the number one reason patients present with the disease. Importantly as clinical trial endpoints or reduction in VOCs are recognized by the FDA, clinicians and

patients as clinically meaningful. Crizanlizumab is a humanized monoclonal antibody and it focuses on p-selectin, which is an important cellular adhesion factor. It has demonstrated reduction VOCs provided by more VOC free days and has demonstrated important and manageable safety profile in clinical trials. The demonstration of efficacy with or without hydroxyurea is likely due to its different mechanism of action. However, unlike hydroxyurea, crizanlizumab does not need to be titrated, patients begin to feel effects within two weeks. No laboratory monitoring is required, and photogenic effects have a shorter washout period, compared to placebo in the same study crizanlizumab showed reduction of VOC over a year time period as well as percent reduction in dates hospitalized. It's administered as a 30-minute IV infusion and adherence can be tracked. Side effects are manageable with the most common including arthralgia, nausea, back pain and pyrexia, and does not require any pre-medication or post-observation. I appreciate your time and look forward to your consideration of Adakveo by the committee today. Thank you for your time.

Jennifer Wheeler: Thank you so much. Anyone else for public comment on either one? Alright, Carl, you can start with a clinical presentation, please.

Carl Jeffery: This is a new class of medications that we're reviewing. Both these products you have heard about already are relatively new on the market. They are Adakveo and Oxbryta. We did receive one letter, I think, from Novartis and Janelle may have already spoke to this information here. As we heard about there are these two new agents that are for the treatment of sickle cell anemia, different pathways and different mechanisms and how they achieve what they are supposed to be doing here. As we heard, it does have major consequences to the hemoglobin and as a result, many organs are impacted, day to day life is impacted with some significant impact and some in a lot of pain. It was probably mentioned, but I just want to reinforce the Adakveo is administered IV every four weeks after titration it is given every two weeks for the first two doses. But the other Oxbryta is given orally once daily. So, we heard about those. Oxbryta increases the hemoglobin, so I think we had this discussion last time with the ESAs as to is that you do not want to push the hemoglobin too high. So, they do have kind of a max limit on those, we have proposed that criteria. Again, I have put together in the Word document our proposed criteria. So, this is all new criteria. There is nothing existing currently in Chapter 1200. So, I do not want to mislead the board. It is all black out here, but it should be. It is all new criteria. So, for Adakveo, we've got the recipient has a diagnosis of sickle cell disease, 16 years of age or older. There is documentation of at least two vaso-occlusive events that required medical facility visits and treatment in the past 12 months. Recipient has a documented history of failure or intolerance to hydroxyurea or L-glutamine, or contraindication to both agents prescribed by or in consultation with a hematologist or oncologist or specialist with an expertise in the diagnosis of management in sickle cell disease. For Oxbryta, is still in the hemoglobin levels. They have a diagnosis of sickle cell disease; recipient is 12 years of age or older. There is documentation of events in the past 12 months, there is documentation that the recipient's hemoglobin level does not exceed 10.5 grams per deciliter prior to therapy. The recipient has documented history of failure or intolerance to hydroxyurea, and prescribed by or in consultation with the hematologist or oncologist or specialist in the diagnosis management of sickle cell disease and then the recertification was there is a positive clinical response and then for Oxbryta we specifically call out the hemoglobin levels are not being exceeded there. I will jump over now to the MCOs criteria that speak to those.

Jennifer Wheeler: Thank you, Carl. So, we will start with Lisa again.

Lisa Todd: Hi, yes, this is Lisa Todd with Anthem. And we agree with Optum's proposed criteria, no additions to suggest and regarding utilization, we don't have any claims for these two new agents. And just utilization in general is pretty low. We only have six members on drugs in this class. Thank you.

Jennifer Wheeler: Thank you, Lisa. We will jump over to HPN, Ryan.

Ryan Bitton: Yeah, we just had a couple of additions, a comment in both products to not have been receiving concomitant blood transfusions or the other product. And then Adakveo, we did have that specialist requirement on there as well. As far as our data, we included hydroxyurea, which we are in a different GPI category. But we, you can see that we have hydroxyurea capsules, some compounded hydroxyurea, as well as the small use of Siklos and Droxia.

Jennifer Wheeler: Thank you, Ryan and Tom, SilverSummit.

Tom Beranek: Both our policies had a lower level for hemoglobin as well. So, for Adakveo, it was greater than four. I think a couple other things have been down by the other plans. Again, not prescribed concurrently with Oxbryta and I have had that the same with Oxbryta and again I have the dose does not exceed here five milligrams. So pretty much it for that. For Oxbryta we got a lower level of 5.5 better than that and less than 10.5. And a dose I see 1500 milligrams for 3 tablets a day. For utilization charts now we don't have any utilization for either one of these drugs.

Jennifer Wheeler: Thank you, Tom. The only thing I think that we should maybe consider, just for consistency purposes is adding in no combination therapy, so they cannot be on both. I know some of the MCOs had that in there. And I think that probably good to maybe put in there. Any comments from board members?

Dave England: David England, I just had one question. I think it was something about, I cannot find it right now. But where it said that these could be given concurrently with hydroxyurea because on 110 of our handout it specifically says they can be. And I know, I remember when I was wherever the skimming through the binder earlier, there is a comment on failure or intolerance of hydroxyurea, but does that mean, but from what I gather on Page 110 of our handout today, it can be given concurrently, I just want to be sure that does not restrict it the way it is worded. Otherwise, I agree with your comment.

Carl Jeffery: My understanding is that it can be used concomitantly with hydroxyurea. Again, similar to the other one, I think we can just add it as an overall criteria to say this approval will be given for single agent

Jennifer Wheeler: I think that's good. Any other comments from board members? I would like to call for a motion to approve this as presented with the small addition of a single agent concomitantly.

Netochi Adeolokun: This is Netochi, I will motion.

Michael Owens: This is Mike Owens, I second.

Board: Ayes are unanimous.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for proton pump inhibitors.

Jennifer Wheeler: Moving on to it looks like just a little change in quantity limits for our PPI drug class. Any public comment on that? Carl, if you want to move ahead with the presentation, please.

Carl Jeffery: Thank you. So, this will be a pretty fast class. This is an established class. I do not think I need to give you all an overview of how they work. But several years ago, the board added some criteria that restricts the concomitant therapy with H2 blockers and Sucralfate, there are a few articles that show there is a clinical benefit for the combination, there are several showing that the combination doesn't cause harm. We do get several hearing requests or inquiries for this criteria. I would just like to propose that we remove the restriction from the criteria. So that criteria would just be no PA is needed essentially if they are taking one a day, so anything over one per day would require prior authorization but it wouldn't be any of the restriction any longer for concomitant therapy with an H2 antagonists for sucralfate.

Jennifer Wheeler: Perfect any comment from any board members? Regarding not taking that off.

Lisa Todd: Yes, Anthem agrees.

Ryan Bitton: As does HPN.

Tom Beranek: SilverSummit thirds that.

Jennifer Wheeler: Any comments from the board?

Dave England: This is David England, I think originally that was my pet peeve anyway, several years ago. I know we see those prescribed concurrently. And it did not seem to make any sense, but it is more of a criteria rather than anything clinically considerations. I appreciate, I can live with this change. Yeah.

Jennifer Wheeler: Can I get a motion to approve the removal of the criteria of non-commitment therapy for sucralfate and H2 antagonists?

Dave England: This is David England, so move.

Netochi Adeolokun: Netochi, I will second.

Board: Ayes are unanimous.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for tobacco cessation products.

Jennifer Wheeler: Thank you. Moving to our next topic, we have updated guidelines, quantity and limits on tobacco cessation product. Any public comment? We have one letter.

Carl Jeffery: Yeah, and this is an old letter. We did get this letter a while ago. It has been circulated to the board. They just asked for us to take a look at the criteria and make sure that it aligns among the MCO's as well. Tobacco use is a pretty major issue and is the leading cause of preventable illness and death in the US. Almost a half a million deaths per year related to tobacco use. Several products are available in the class from nicotine replacements, and then such as Chantix. It is a partial neuronal alpha-4 and beta-2 nicotinic receptor agonist and so it prevents nicotine stimulation. Let me pull up the criteria that we had proposed here on smoking cessation. What we have is in Chapter 1200, is not the complete criteria because we don't list quantity limits specifically in Chapter 1200. But if you look in the pharmacy billing manual, Appendix D, there is a limit of 180 days per rolling 365 days for any product and this is across the board. I do not have any proposed changes to this criteria. I think the utilization is reasonable, nicotine patches being far more utilized. The nicotine patches, the transdermal system, by far the most popular

with Chantix actually is being used more than I thought because I remember when it first came out there was some side effects. They were not always favorable. But the Chantix really is only indicated for initial treatment of 12 weeks, and then they can get an additional 12-week course on that if it will increase their likelihood of success. And so, 180 days per year, I think is still completely reasonable and it is much more than a lot of other states and payers allow to, so I think it's pretty generous with the state.

Jennifer Wheeler: Perfect, thank you Carl. Lisa with Anthem.

Lisa Todd: This is Lisa Todd with Anthem. We agree with the criteria the only thing that we have for Anthem is really around our PDL. And we do cover Chantix, we cover you know all of those, looking at our utilization kind of the same as Fee-for-Service that patches are the number one and then you know Chantix and then down to the bupropion but I really do not have any other comments. Thank you.

Jennifer Wheeler: Thank you, Lisa. Ryan HPN?

Ryan Bitton: Yeah, we approved QL criteria, adjustments and with 180 days per year, which is similar to how we have it. Our utilization shows the patches we combined everything into the patch and lozenge so it's a little bit easier to see here the patches is definitely most highly utilized following by followed by Chantix both the starting and continuing month packs, so they have I think equalization for HPN.

Jennifer Wheeler: Thank you, Ryan. Tom, SilverSummit.

Tom Beranek: We agree with the criteria presented here. Again, really nothing further to add to Ryan, Lisa or Carl have not already stated. Usage is not out of the ordinary.

Jennifer Wheeler: Perfect, thank you. Any comment from the board? I would like to get a motion to approve the criteria as presented by Optum.

Netochi Adeolokun: This is Netochi, I will motion.

Brian Le: Brian Le, second.

Jennifer Wheeler: Thank you very much. We'll move to vote.

Board: Ayes are unanimous.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Toradol® (ketorolac tromethamine) tablets.

Jennifer Wheeler: Thank you, moving on to the next we will be looking at ketorolac or Toradol. Any public comment? Carl, if you would like to start with a clinical presentation, please?

Carl Jeffery: The ketorolac products are being brought to the board today because it is been a long time since this criterion was last reviewed. I do not think we have an actual recorded date of when it was last reviewed. We were working on the Chapter 1200 to make sure that all of the criteria are current and has been recently reviewed. So, we just brought this to the board. Ketorolac is indicated for the short-term treatment, less than five days, of management of moderate to severe acute pain. The oral dosage form is only intended to be a continuation of IV or IM therapy. The oral dose should not be given as the initial dose. The five-day limit is due to increased risk of GI bleeding, and there is a concern for renal toxicity.

The utilization showing about 1,300 claims per month that we are seeing here, the quantity limit, calculate this out is about 2.6 tabs per claim on average. So, the utilization looks appropriate from our side. I do not have any proposed changes to the criteria, but you can see that what we are looking at here is the last review by the DUR Board was prior to probably 2010 sometime so it has been 10 years since this has been reviewed.

Jennifer Wheeler: Thank you, Carl. Lisa, Anthem.

Lisa Todd: I did not really have any comments regarding the Optum criteria. It appears that I did not fill out a form for that, if I need to do that and submit that, and I will did not see any criteria, you know, proposed changes. So, I did not do the form but may have just missed that. But anyway, our utilization we have 847 members on this. You know, we agree with Optum and don't really have much to share.

Jennifer Wheeler: Thank you, Lisa. Ryan, HPN.

Ryan Bitton: We agree with criteria change. Lots of folks in the tab there.

Jennifer Wheeler: Thank you, Tom, SilverSummit.

Tom Beranek: Nothing really to call out on utilization chart. We are good to here.

Jennifer Wheeler: Any comments from the board members?

Holly Long: This is Holly, I have a question based on the utilization that you are looking at Carl, you are saying that Optum is proposing no changes? Is it based off of looking at that? Do you think that this is one of those where the prior authorization is not needed, and the board can consider removing it? Or are you saying we should just leave it the way it is because it is doing its job?

Carl Jeffery: I think the quantity limit is doing its job and so I think it is effective, I would not change it.

Jennifer Wheeler: Carl, the only question I had was regarding max dose per day. I have seen this in practice a lot is where they will get discharged, say from the hospital and be given 30 tablets, but it is at a max dose of 40 milligrams per day. So, then it would be a longer duration. Do you think that we should maybe add on some kind of quantity limit with that or any thoughts on that from anyone?

Carl Jeffery: Yeah, I would not be opposed to adding a max of 40 milligrams per day.

Jennifer Wheeler: So then for that five-day period they would be getting 20 tablets.

Carl Jeffery: Yeah, and we could even add a per day max I think is worthwhile.

Jennifer Wheeler: Okay. Any comment from the board regarding that?

Netochi Adeolokun: This is Netochi. I agree with that. I like that we have a max of 20 tabs a day with that.

Jennifer Wheeler: Can I get a motion to approve the criteria as with the addition of no more than 40 milligrams per day?

Michael Owens: I motion, this is Mike Owens.

Brian Le: Brian Le, second.

Jennifer Wheeler: Thank you. Move to vote.

Board: Ayes are unanimous.

5. Public Comment on any DUR Board Requested Report

Jennifer Wheeler: Thank you very much. Now we can move into any public comment on any of the board reports that we have requested. Carl, do you want to go ahead and start the presentation on the DUR requested board report?

6. DUR Board Requested Reports

a. Opioid Utilization – Top Prescribers and Members

Carl Jeffery: On Page 169, if you are following along the binder, this is where we have our standard opioid utilization report. This is the same are used to seeing shows the count of claims and trend through 2019. So, a downward trend. It's still a good trend. If we look on Page 170. The utilization broken down by the sum of morphine equivalent doses, and the total and the morphine equivalent dose per day supply. In the last column over here shows you the MED per day supply. And I have trended that over the year as well. And both of those are trending downward. If we have a sum of even the total sum of MED fluctuates a little bit, still, the overall trend is heading down. Then we get into the opioid utilization by prescriber for the top 10. I'm showing quarter three of the top ten. We talked last time about looking at morphine equivalent dose per day supply. And when I ran that, the numbers that came up here are really skewed. I am not sure that this is the most viable way to look at things. I think we have got for either one off, here is what we got, you know, one member and one claim for two days supply showing these really high. I think this one specifically was a fentanyl. If I remember correctly, I think it was for a hospice patient or in long-term care. I am not happy with how those numbers showed up. I still ran at the same old way of doing it by the total morphine equivalent dose here too. So down below, we see the quarter three, which is what we saw last month. Try to get both of these on the screen at the same time, comparing this quarter three to 19 by total MED by the bottom graph here, quarter four by total MED. We could see that the prescribers line up. We have got prescriber A is still on here, a couple new ones for quarter four. So, a lot of pain specialists, a lot more MDs we are seeing in the top here then what I think what we saw in quarter three, so a lot of them were PAs were the top ones. Top utilization by member and again, we did this MED by member too, so we have these other members. And again, methadone products are not included in here because they are on that sliding scale. They are hard to calculate. So, the members here and then what they correspond to down below. This may be easier to see. You see like the 67,000 MED, that they are getting their total for the quarter go down and find that that number down here we can see that they are on a fentanyl patch, and then on methadone as well. They only got one claim of methadone for 150 tablets and then oxycodone. That is it, our next report is methadone, but I will pause for questions and then we can pass it over to the MCOs.

Jennifer Wheeler: Any questions by the board? Carl, I agree with you. I am not sure that I like the change and doing it by the morphine equivalent, I feel like it is kind of a skewed report that might not be necessary. Anybody else has any comment on that?

Dave England: This is David, I think it was my request, look at the morphine equivalents. And a lot of places I am looking at now, you know, we have to provide, even though you are decreasing your use, what

are you increasing the use per individual rather than count? And it is kind of a strange number. I have a hard time understanding that I am going have to take a look at something else again, but I am so glad to see the trends is going down. But yeah, the numbers look kind of strange, but it is interesting to think about these. Thank you. Appreciate it.

Brian Le: This is Brian Le. So, when I looked at this, I mean, I am a pain specialist. I look at a number a little bit different. I see the total morphine equivalent dose and to me, I am more interested to know how much they take per day per patient per day, the total number might be really high, the trend has been going down, which is good. And I think that is what we are looking for. But to show that some member getting up to like 300 morphine, take people and dose per day, the scary dose, unless they are in hospice, or they have significant opiate dependency, I do not see any reason why anyone should go up to that dose because it does get into the dangerous dose. I looked at the both ways. I think, as a doctor, when I looked at the dose, we want to see exactly how much per person per day, but we can see when it's become dangerous to the patient.

Carl Jeffery: Yeah, and I think that is a good point. And I think the one thing that I did take away from this report is so if you look at the numbers over here, the highest we are seeing is 270 morphine equivalent. And this is per, per member per day. So, it is not super crazy, I think 270 is, I mean, it is, this is really high, but you are looking at the prescriber on here and their top two here, oncology and pain.

Brian Le: If we look at the guidelines for the opiate right now, on the guidelines call for 90 MED or less, so even like 200 or 180 is too high.

Carl Jeffery: Yeah, certainly, we can take away any kind of recommendations from the board, you know, maybe contacting, doing some education to these providers. I see the oncology specialty and I am not sure like what kind of response we would get sending letters to the oncology doctor saying you are showing a lot of MEDs per member per day?

Dave England: Yeah, I think I would like to see them, I would like to maybe try for a few more months, we will see if the numbers mean anything to us or take a look because I agree, the numbers I am looking at it, anything over 90 a day is when you got problems, anything less than that is, is an improvement. But again, this one has a number and not knowing why and how the numbers coming to us might be misleading. So, it would be interesting to see what else we can perceive from this as opposed to just, I do not like the number let us not do it anymore. And we do have a couple more months and see if it means if it looks like it is doing anything and then if not, we can regroup and relook at it again. But I do appreciate this. The numbers though. It is somewhat helpful.

Brian Le: I agree to that. Thank you.

Jennifer Wheeler: I agree too. Lisa with Anthem.

Lisa Todd: Yes. One thing I want to mention about these reports is just in general, is that with Anthem, and I think most of our plans have, the opioid PA criteria. So, members that do have, cancer diagnosis, have sickle cell or in hospice. And those members are excluded from the long acting PA criteria. So, and those numbers are included in these reports. So, some of these high numbers might be those very patients. But if we go to my first report about the opioid utilization, kind of the same idea if you look at the member count from January to December it has decreased just slightly, the claim count has decreased slightly and claims per member went down just very, very little. So, kind of the same kind of the same picture that Fee-for-Service had. Then if you go to my next report is the top opioid providers by claim

volume. This is the fourth quarter data is the first chart and then the next chart is the third quarter data. What I did, the highlighted yellow are providers that are in both of those categories that they are the same provider in the top 10 in both of those quarters, so, we do have consistency that eight of the providers are the top eight in the top 10 are consistently in this in the top 10. That is an observation and then the top 10 opioid utilizers um, I went and let me see, I do have some of the MME, but I think it was a kind of struggled with a calculation. I think if some of these drugs did not have like whether it has N/A, that NDC did not have a conversion factor automatically built in. So that is why it says non applicable. And so, there is my top 10 for the fourth quarter. Methadone. Did we talk about methadone? I think Carl did.

Carl Jeffery: No, that is the next report we will get to.

Lisa Todd: Okay, so that is it for me for opioids. I do not know if anyone has any questions.

Jennifer Wheeler: Any questions for Lisa? Alright, we will pop over to Ryan with HPN.

Ryan Bitton: Okay, thank you. Yeah, you can see our chart looks similar to the others. I mean, I agree with the whole conversation about MME. Its utility and how you need to look at it. But we also included the benzo claim count, because that was in there previously. That is just kind of been a hold over you can see the trend similar to the others, MME and the total opiate scripts kind of go together and we look at that by month, go then scroll down. We have the same top ten in prescribers. For Q4, and Q3, you can see that they is both of the same, but we had a two more and two dropped off from Q3 to Q4, or vice versa. You go to the next one. That is the top 25 Members using opioids we highlighted in light blue if the provider was in the top ten and so we refer to that. Also, we listed that if they were on benzos and if that benzo provider was in the top ten benzo provider, there is only one, one of those and Number 14, it looks like and then finally, there is the opioid and benzo summary. As you can see, look at the numbers decreasing in opioids decreases in benzos and decreases in the combination of both of those on Slide 29. Are there any questions?

Jennifer Wheeler: Alright, any questions for Ryan? We will move over to Tom with SilverSummit.

Tom Beranek: Not a lot on this chart, we have been pretty flat actually, unfortunately, we have not seen quite the downward trend the other two plans and Fee-for-Service has had, we are not really going up either, it is just sort of sitting at the claim counts going up just a little bit. That is mostly due to the number counting. You can see in January, we had about 201 members prescription so that is why the claim count is up, but still pretty steady state. I agree with everything everybody said about MME. Top opioid prescribers, the top eight for the current quarter were also in the previous quarter bottom two are new. There were 1,969 opioid claims for the current quarter the top ten opiate prescribers prescribed 1,506 of them 260 of those claims were by the top opioid prescribers. They were in for less than a 20 days supply, which is good news. The bad news is they get more than those 20 days supplies and then you have more claims. I have highlighted there also where it is kind of purplish pink. Those are members who are getting their narcotics from one of our top ten opioid prescribers. We only actually got two of them, we will go to utilization by members.

b. Methadone utilization and place of service

Carl Jeffery: Right, the next report we have here so the board asked us to take a look at the methadone utilization. Page 173 in the place of service, so the retail chain pharmacies are dispensing most of the methadone in Nevada from Fee-for-Service, like the Walgreens and CVS and Walmart's are seeing most of that. We will not see treatment centers because they are paid on a daily rate so they do not bill

separately for their medication so it does not come through to us so what we see here is just I think technically they have to be methadone for pain to be dispensed from a retail pharmacy. I do not think a pharmacist can knowingly dispense methadone for addiction treatment from a retail place. I think these are all being used for pain. You can see the breakdown is pretty interesting like the chain stores here. The ten and five milligram tabs are certainly the most popular methadone. Any questions or comments on that one?

Jennifer Wheeler: Does not sound like it. We can move over to Lisa, for Anthem.

Lisa Todd: Great, thank you. For our methadone utilization, I did pull our retail claims. And just like Carl said that pharmacists at the retail setting can only dispense for pain. So, we had 175 members that are receiving the methadone. I did break down of those 175 members the type of pharmacies that they are receiving those from. Obviously, the majority of them are the community or retail. You know, like the Walmart's and the CVS's and those like Carl was mentioning, we have a few long-term care and one clinic pharmacy. I went ahead and reached out to my medical claims, these would be the methadone type clinics. And so, these would not be used for pain these would be used for the addiction piece of it. We had 955 claims. So, we have 161 members that are utilizing our methadone clinics in Nevada. That concludes my methadone report.

Jennifer Wheeler: Thank you. Any questions for Lisa? Alright. Ryan HPN.

Ryan Bitton: At the top we have the place of service medical and the same kind of conversation that Carl gave, there is data from the people that are involved in methadone clinics, but do not have that pretty count that we would see a similar to pharmacy. So, we have the same thing. Most of it is done in the retail chain. We did carve out the retail independent as well just to look at the distribution there. And grand total of 1,000 members, the distribution and then ten milligram is by far the one most used and a little bit of the five milligram.

Jennifer Wheeler: Thank you, any questions for Ryan? Tom, SilverSummit.

Tom Beranek: We only had two, the methadone used, the five milligram and ten milligram, more ten than five same as everybody else here 49 total members. I see a discrepancy of one here. I am not sure what that is, but 42 of them were chain stores which is kind of what we are seeing from the others as well the large contingent of them and then six went to retail pharmacy and from a claim count, you know, they are almost identical to throughout the year for both of them. The tens went up a little bit in September and down a little bit and November so you know, maybe they got double fills at the end of September and then get a fill in October so it might last to end of November. But pretty steady throughout the year.

c. Antibiotic utilization

Jennifer Wheeler: Any questions for SilverSummit? Alright, Carl, you want to start with the antibiotic utilization?

Carl Jeffery: So, this is I think our last report from the board requested reports. This is a busy slide that goes on for three pages. But it is sorted by the top count of claims of antibiotics. During the meeting on July 26 of 2018 the DUR board voted to add some PA criteria for third generation cephalosporins, fluoroquinolones and oxazolidinones. This was effective March 4, 2019. When we get down to the graphs, and I think this put them in a different order than they are listed in the binder, but if we look at the antibiotics with PAs, see the ones over here, the Cefdinir, ciprofloxacin and the levofloxacin. March really

was a big drop. And this was definitely obvious when we implemented the criteria. This ceftriaxone still is number one. And this one did not get was not affected because it is administered by a physician. It did not have the PA criteria applied to it. But you can see that mostly they have stayed the same. It is interesting to see that they did not really jump back up until we get back into cough and cold and flu season, again in October, but you would expect that maybe it would drive the utilization up. So, if this dropped, it had to go somewhere else in March here, like I would expect to see a big spike here. And I guess there is a couple spikes here that these other medications here, like Sulfatrim and amoxicillin, but not really much. And then if you compare, just the number of claims in January from 2019 to December, pretty much down across the board, which I think is an indicator that we are in our initiatives, even though we did not apply them on all these medications. We are still getting the word out about antibiotic resistance and kind of a stewardship program, not only from the Medicaid standpoint, but I think just as a general push, there has been more information disseminated to providers about using antibiotics judiciously and I think that was a big benefit. I am encouraged by these numbers. We had when we implemented this, we had some complaints and you know, end of the world, Chicken Little, the sky is falling type claims. And after the initial couple months, we really have not heard much complaint about it. Any questions I can field from you?

Dave England: This is David, I like the numbers, it is nice to see that this is an idea what the flow is and how we are doing because I know, hospitals are pushing big time, you know, antibiotic stewardship, but at the same time, it is kind of nice to see what is going on out in the public sector, so to speak, out in the retail world, if the same thing is holding true there as well. And this appears to be the impression that the word is getting out that antibiotics are not the answer to everything for infections.

Carl Jeffery: Yeah and I think what is really going to be telling we do not have access to this data, the MIC, then you know, the resistance to these antibiotics that we put restrictions on, you know if that is improving, that is going to be where the indicator is.

Dave England: Thank you for doing this. Appreciate it.

Carl Jeffery: And I do not know. We can go through these the MCO's did not adopt the same criteria, the PA criteria. I do not think any of them adopted the PA criteria that Fee-for-Service did. It's I am not sure the numbers are going to be that impactful.

Lisa Todd: So, the only thing that I would say would just kind of be, you know, high level but to Carl's point, Anthem did not adopt PA criteria for the antibiotics. But it is kind of interesting to me that our top couple drugs match like Fee-for-Service, like our amoxicillin and azithromycin and amoxicillin for us was about 38% of the claim counts and yeah, but that is all I had to add.

Jennifer Wheeler: Thank you, Lisa. Ryan, did you want to go over yours?

Ryan Bitton: There is not much to really add, you get a similar trend in the scripts. And just to confirm we did not implement the same criteria change that Fee-for-Service did.

Carl Jeffery: It is interesting though, the numbers on these graphs are so similar. I like that they are seeing the same number. So, I think that this stewardship message is getting out on the antibiotics. And I think even though HPN did not adopt the same criterion, the communication to the prescribers, the numbers are still lower.

Jennifer Wheeler: Thank you. Tom, did you want to speak about yours briefly?

Tom Beranek: I was going to point out the ciprofloxacin and 500mg. So, it is the gray line there and the far right at the bottom. So, you know, to Carl's point even though we did not adopt the criteria, it seems like it is working, the message is getting out there so to speak is that particular drug it was up around 100 claims in January and then slowly throughout the year went down what you would expect obviously, during the summer months, and whatnot, but then even in November and December when some of the other ones started to climb that one continued to sort of a downward trend. So that was really the only thing I wanted to point out from ours.

7. Public Comment on any Standard DUR Report

Jennifer Wheeler: Thank you, Tom. And any public comment for the standard reports included? We will move into those. And Carl, do you want to go over the standard report with review of prescribing program trends?

8. Standard DUR Reports

Carl Jeffery: These are the standard reports, the same ones we see at every meeting. I will try to keep this brief. I know we are going a little long here. No surprise, the top ten drugs by paid amount are the top line for the current quarter, so fourth quarter, and third quarter 2019 antihaemophilia products are always our number one by a long shot. We have added some PA criteria to these to try to get some management around these, but they are still very highly used and expensive medication. Followed by the antiretrovirals, insulin which politically is out there, and people are aware of this, but it is number three spend. Sympathomimetics, which is albuterol mostly. And then we move down to anticonvulsants. When we get down to the claim count, anticonvulsants, it was not that long ago when we saw opioid products up here in the number one. So, it is encouraging as well to see that opioid numbers drop here. It has been replaced by the anticonvulsants. I think a lot of prescribers are shifting over from writing a lot of opioids to putting people on mostly gabapentin and a lesser extent Lyrica. But there is really nothing that I would not consider out of the ordinary and these. I will pause for some questions before I move to the next one.

Jennifer Wheeler: Any questions or comments? Alright.

Carl Jeffery: The last one here is just our proDUR activity in what you were asking about Jen, was some of the drug-drug interactions that are identified. We process all of the physician administered, we price, the physician administered drug claims, and we kind of shoehorn this duplicate Rx in to checking for duplicates for those PAD claims. So, some of these numbers are going to be a little bit skewed for this one, this duplicate, see the number of paid claims on here is only 26%. So that is probably due to that. But the drug-drug interactions and duplicate therapies are much higher, and we look at the percentage paid so still even the drug-drug interaction of 72% of the claims are paid. So, they have to enter an override code to say, yeah, we realize that there is an interaction and move forward. The rest of the charts here are not user friendly for, especially for the online format. So, I am not going to spend any time going through. It is in your binder. And if you do have any specific questions, let me know. We did a couple retroDUR activities. And last quarter was the triptan without having a preventative therapy. So, if they were receiving regular triptan without other treatment, we sent out letters. Then Hep-C treatment, after they completed. We sent letters out to the providers asking, was treatment successful? Do you finish treatment, did you draw viral load after therapy was completed?

Jennifer Wheeler: Thank you, Carl. Any questions on any of the standard reports? Alright, Lisa with Anthem?

Lisa Todd: I'm kind of comparing to the Fee-for-Service criteria. My first reports are the top ten drug classes, and these are sorted by paid amount. The difference is that our number one third quarter and fourth quarter, actually, over the whole year has been the antiretroviral. This is kind of due to, I think that they are in our top ten drugs, if we broke it down by drugs overall, there are five new HIV meds. A lot of them are consolidating different regimens into one pill or a one capsule kind of treatment. But anyway, they are very pricey and obviously, are being used. Then we are just looking at our drug classes. They remain pretty consistent. As far as the ones with paid amount. There are a few, like the MS agents climbed a little higher in the category but they are still in our top ten. If I go down to the top ten by claim count, so this is where it does shift and it has been consistent over the year also, that the NSAIDs are the number one, and then our opioid combinations are still in our top ten by claim count, but they are quite a bit lower. And looking back over the years, before we put in the PA criteria, those opioid combinations were a lot higher in this claim count. And if you compare looking at the opioid combination, the claim counts from the third quarter and the fourth quarter. It actually it has increased just a little bit. I don't know of a specific reason why, if that was drilled down to a few more members or that type of thing, but anyway, it is still lower on the chart. If I go down, there is just the standard proDUR similar to like Fee-for-Service. And then the top ten drugs for the proDUR. Those remained consistent looking at past reports. No red flags or really any changes there. And then, retroDUR, I cannot remember if Carl talked about this, but one of the things that we did talk about in our clinical programs, and this is where we outreach to members and providers, we talked about gaps in care. And this is on different topics, whether it be adherence or asthma, cardio as the whole, just any of those high risk things, we actually felt pretty good about the response rate, we had a 28% positive outcome of that in changing in prescribing habits, whether it be they are becoming more adherent or getting their meds more or they added the extra drug or they discontinued regarding the drug-drug interaction. But that is kind of it as a high level.

Jennifer Wheeler: Thank you, Lisa. Any questions? Alright, Ryan, HPN.

Ryan Bitton: Okay, similar, a little bit more of an eye chart, in the template format. First up in Excel, so you can see we get the opioid chart again, opiate prescription will be skipped because this is kind of duplicative. The second page, very similar to what Lisa was showing with antiretrovirals, being the top, insulin, cancer and diabetes kind of being in that top section. Looking at claim count also, NSAIDs and you know, we got the anticonvulsant, which is kind of matching Fee-for-Service. So, everything is kind of expected here, opioids still there, but they are much lower than they were previously. This goes into our retrospective DURs. Ours you can see some of the common dose per day just like therapy, drug-drug interactions, drug-disease, etc. Then we get to the bottom of this page and the next page is our gaps in care. We spelled them out specifically for asthma, cardiovascular, you can see that those contacts, responses and response rates as well. The last page goes through and talks about last few gaps in care. And then the final page talks about our proDUR and the categories and the drugs that are firing there. So, nothing new. We did enhance cardiovascular gaps in care section, with our retrospective DUR beyond that. It is kind of the same program.

Jennifer Wheeler: Thank you. Any questions? Okay, we'll move over to Tom.

Tom Beranek: Right. Thanks, Jennifer. Yeah, I do not think we have anything different or unusual here with what you see from the top ten paid amounts, they were exactly the same drugs for both this quarter and the previous quarter, a couple of them switched spots, similar to everyone else, the antiretrovirals, insulin at the top. Claim counts, and then non-steroidals, anticonvulsants, are similar to both the other plans with Fee-for-Service opioids are slowly moving down as well. Nothing differently to call out there. RetroDUR numbers, ingredient duplication and high dose at the top.

9. Closing Discussion

Jennifer Wheeler: Thank you, Tom. Any questions from the Board? Is there any public comment? Our next meeting is scheduled for July 23, 2020. Meeting adjourned. Thank you.

Meeting adjourned 3:46 PM.

Clinical Presentations

Prior Authorization Guideline

Guideline Name	Psychotropics for Children and Adolescents - Antipsychotics - Antidepressants - Mood Stabilizers (including anticonvulsants) - Sedative Hypnotics - Antianxiety Agents

1 . Criteria

Age	Members less than 18 years of age
Approval Length	30 days for initial request of cross tapering/discontinuation with requested agent, 6 months for discharge from an institutional facility on the requested agent, 6 months for stabilization on the requested agent without history of a previous authorization, up to 1 year for all others
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following:

1.1 The patient has been discharged on the requested agent from an institutional facility in the last 30 days (name of facility and date of discharge must be provided)

OR

1.2 There is documentation that the patient has been started and stabilized on the requested agent and the patient has not previously received an authorization

OR

1.3 All of the following:

1.3.1 There is documentation in the patient's medical record that the requested psychotropic medication is part of a comprehensive treatment plan that addresses education, behavioral management, living home environment and psychotherapy

AND

1.3.2 One of the following:

1.3.2.1 For patients who are in initial treatment (treatment-naïve) or are continuing therapy that is considered unstable (dose change in the last 3 months):

- Medical documentation supports visits with the physician or prescriber at least monthly

OR

1.3.2.2 For patients who are continuing therapy that is considered stable:

- Medical documentation supports visits with the treating physician at least every 3 months

AND

1.3.3 If the patient is less than 6 years of age, the indication for the requested medication is verified to be medically-accepted as established by the FDA and/or peer-reviewed literature (document diagnosis for use)

AND

1.3.4 One of the following:

1.3.4.1 There is no history of other psychotropic medications in the same therapeutic class (intra-class poly-pharmacy) and fewer than 4 psychotropic medications total in different therapeutic classes (inter-class poly-pharmacy, including the requested agent) within the last 60 days

OR

1.3.4.2 All of the following:

1.3.4.2.1 There is history of other psychotropic medications in the same therapeutic class (intra-class poly-pharmacy) and/or at least 4 psychotropic medications total in different therapeutic classes (inter-class poly-pharmacy, including the requested agent) within the last 60 days

AND

1.3.4.2.2 Each psychotropic medication prescribed is independently treating a specific symptom and/or diagnosis (please document symptom or diagnosis for each agent)

AND

1.3.4.2.3 All psychotropic medications are utilized for a medically accepted indication as established by the FDA and/or peer-reviewed literature

AND

1.3.4.2.4 The patient has had a trial of each individual medication alone and the reason for inadequate response is documented in the medical record

AND

1.3.4.2.5 One of the following:

1.3.4.2.5.1 The requested medication(s) will be used for cross-tapering and/or one or more of the previously prescribed agents will be discontinued

OR

1.3.4.2.5.2 The requested medication will augment the effect of another psychotropic medication and both of the following:

- The purpose of poly-pharmacy is clearly documented in the medical record
- Each agent is supported by individual authorizations

Nevada Medicaid

Summary of Psychotropic for Children
Fee For Service
April 1, 2019 - March 31, 2020

Count Of Class	Count Of Members
5	5
4	137
3	633
2	1417
1	3311

Children on All Five Classes

Member ID	Age Band Description	Anticonvulsants	Antidepressants	Antipsychotics	Anxiolytics	Sedative Hypo
A	Age 10-19	LAMOTRIGINE	BUPROPION HYDROCHLORIDE ER (SR)	ARIPIPRAZOLE	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	LAMOTRIGINE	BUPROPION HYDROCHLORIDE ER (SR)	ZIPRASIDONE HCL	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	LAMOTRIGINE	TRAZODONE HYDROCHLORIDE	ARIPIPRAZOLE	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	LAMOTRIGINE	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	TOPIRAMATE	BUPROPION HYDROCHLORIDE ER (SR)	ARIPIPRAZOLE	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	TOPIRAMATE	BUPROPION HYDROCHLORIDE ER (SR)	ZIPRASIDONE HCL	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	ARIPIPRAZOLE	HYDROXYZINE PAMOATE	TEMAZEPAM
A	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	HYDROXYZINE PAMOATE	TEMAZEPAM
B	Age 10-19	OXCARBAZEPINE	TRAZODONE HYDROCHLORIDE	RISPERIDONE	HYDROXYZINE PAMOATE	MIDAZOLAM HCL
B	Age 10-19	OXCARBAZEPINE	TRAZODONE HYDROCHLORIDE	RISPERIDONE	LORAZEPAM	MIDAZOLAM HCL
B	Age 10-19	VIMPAT	TRAZODONE HYDROCHLORIDE	RISPERIDONE	HYDROXYZINE PAMOATE	MIDAZOLAM HCL
B	Age 10-19	VIMPAT	TRAZODONE HYDROCHLORIDE	RISPERIDONE	LORAZEPAM	MIDAZOLAM HCL
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	LATUDA	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	LATUDA	HYDROXYZINE HYDROCHLORIDE	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	LATUDA	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE ER	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE ER	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	CLONAZEPAM ODT	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	LATUDA	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	LATUDA	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE ER	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	QUETIAPINE FUMARATE ER	LORAZEPAM	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	HYDROXYZINE HCL	ZOLPIDEM TARTRATE
C	Age 10-19	TOPIRAMATE	TRAZODONE HYDROCHLORIDE	ZIPRASIDONE HCL	LORAZEPAM	ZOLPIDEM TARTRATE
D	Age 5-9	DIVALPROEX SODIUM ER	TRAZODONE HYDROCHLORIDE	ARIPIPRAZOLE	LORAZEPAM	MIDAZOLAM HCL
D	Age 5-9	DIVALPROEX SODIUM ER	TRAZODONE HYDROCHLORIDE	CHLORPROMAZINE HCL	LORAZEPAM	MIDAZOLAM HCL
D	Age 5-9	DIVALPROEX SODIUM ER	TRAZODONE HYDROCHLORIDE	GEODON	LORAZEPAM	MIDAZOLAM HCL
D	Age 5-9	DIVALPROEX SODIUM ER	TRAZODONE HYDROCHLORIDE	OLANZAPINE	LORAZEPAM	MIDAZOLAM HCL
E	Age 10-19	LAMOTRIGINE	ESCITALOPRAM OXALATE	QUETIAPINE FUMARATE	HYDROXYZINE PAMOATE	MIDAZOLAM HYDROCHLORIDE

Nevada Medicaid

Antidepressant Utilization Top 5

Fee For Service

April 1, 2019 - March 31, 2020

Member Age Band	Age Band Description	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
B	Age 1-4	FLUOXETINE HYDROCHLORIDE	7	7	210	255
C	Age 5-9	SERTRALINE HCL	447	447	14,015	14,530
C	Age 5-9	TRAZODONE HYDROCHLORIDE	420	420	14,804	16,667
C	Age 5-9	FLUOXETINE HYDROCHLORIDE	284	284	9,264	10,702
C	Age 5-9	ESCITALOPRAM OXALATE	76	76	2,580	2,505
C	Age 5-9	MIRTAZAPINE	63	63	2,114	2,150
D	Age 10-19	SERTRALINE HCL	3,008	3,008	94,194	103,876
D	Age 10-19	TRAZODONE HYDROCHLORIDE	2,324	2,324	72,227	83,629.5
D	Age 10-19	FLUOXETINE HYDROCHLORIDE	1,629	1,629	53,153	67,467.5
D	Age 10-19	ESCITALOPRAM OXALATE	1,278	1,278	40,081	41,232
D	Age 10-19	SERTRALINE HYDROCHLORIDE	1,093	1,093	34,276	44,438

Nevada Medicaid

Anxiolytic Utilization Top 5

Fee For Service

April 1, 2019 - March 31, 2020

Member Age Band	Age Band Description	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
A	Age <1	HYDROXYZINE HCL	7	7	77	688.459
A	Age <1	DIAZEPAM	7	7	168	694
A	Age <1	LORAZEPAM	1	1	30	20
A	Age <1	LORAZEPAM INTENSOL	1	1	30	30
B	Age 1-4	HYDROXYZINE HCL	107	107	2,274	22,164
B	Age 1-4	DIAZEPAM	83	83	2,318	9,132
B	Age 1-4	LORAZEPAM	64	64	135	225
B	Age 1-4	HYDROXYZINE HYDROCHLORIDE	3	3	90	180
B	Age 1-4	DIAZEPAM INTENSOL	1	1	25	90
C	Age 5-9	HYDROXYZINE HYDROCHLORIDE	148	148	4,763	7,821
C	Age 5-9	DIAZEPAM	132	132	2,908	17,906
C	Age 5-9	HYDROXYZINE PAMOATE	125	125	4,168	5,673
C	Age 5-9	HYDROXYZINE HCL	116	116	2,661	17,561.25
C	Age 5-9	LORAZEPAM	95	95	473	556
D	Age 10-19	HYDROXYZINE HYDROCHLORIDE	996	996	28,585	53,829
D	Age 10-19	HYDROXYZINE PAMOATE	900	900	26,268	50,475
D	Age 10-19	BUSPIRONE HYDROCHLORIDE	553	553	16,990	35,591
D	Age 10-19	HYDROXYZINE HCL	314	314	8,740	35,193
D	Age 10-19	LORAZEPAM	305	305	3,219	6,103.75

Nevada Medicaid

Antipsychotic Utilization Top 5

Fee For Service

April 1, 2019 - March 31, 2020

Member Age Band	Age Band Description	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
B	Age 1-4	RISPERIDONE	38	38	1,131	1,299
B	Age 1-4	CHLORPROMAZINE HCL	6	6	164	649
B	Age 1-4	RISPERIDONE ODT	2	2	60	90
B	Age 1-4	PROCHLORPERAZINE MALEATE	1	1	20	30
B	Age 1-4	PROCHLORPERAZINE EDISYLATE	1	1	1	2
C	Age 5-9	RISPERIDONE	1,876	1,876	60,829	103,298
C	Age 5-9	ARIPIPRAZOLE	1,082	1,082	32,885	41,952
C	Age 5-9	QUETIAPINE FUMARATE	218	218	6,663	11,223
C	Age 5-9	ZIPRASIDONE HCL	91	91	2,656	3,736
C	Age 5-9	RISPERIDONE ODT	84	84	2,632	4,038
D	Age 10-19	ARIPIPRAZOLE	4,102	4,102	124,796	147,278
D	Age 10-19	RISPERIDONE	3,974	3,974	120,992	220,631.5
D	Age 10-19	QUETIAPINE FUMARATE	2,470	2,470	74,651	101,186
D	Age 10-19	OLANZAPINE	787	787	22,611	29,470.5
D	Age 10-19	LATUDA	686	686	19,691	21,244

Nevada Medicaid

Sedative/Hypnotic Utilization Top 5

Fee For Service

April 1, 2019 - March 31, 2020

Member Age Band	Age Band Description	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
A	Age <1	PHENOBARBITAL	39	39	1,241	8,461
A	Age <1	MIDAZOLAM HYDROCHLORIDE	2	2	2	3
B	Age 1-4	PHENOBARBITAL	150	150	4,474	51,530
B	Age 1-4	MIDAZOLAM HYDROCHLORIDE	41	41	41	75.66
B	Age 1-4	MIDAZOLAM HCL	13	13	71	382
B	Age 1-4	DEXMEDETOMIDINE HCL	4	4	4	8
C	Age 5-9	PHENOBARBITAL	140	140	3,875	85,048
C	Age 5-9	MIDAZOLAM HYDROCHLORIDE	50	50	50	114
C	Age 5-9	MIDAZOLAM HCL	22	22	22	49
C	Age 5-9	DEXMEDETOMIDINE HCL	4	4	4	8
C	Age 5-9	ZOLPIDEM TARTRATE	1	1	30	30
D	Age 10-19	PHENOBARBITAL	177	177	5,050	86,565
D	Age 10-19	MIDAZOLAM HYDROCHLORIDE	54	54	54	119.5
D	Age 10-19	MIDAZOLAM HCL	42	42	42	90
D	Age 10-19	ZOLPIDEM TARTRATE	21	21	586	616
D	Age 10-19	TEMAZEPAM	1	1	15	15

Nevada Medicaid

Anticonvulsant Utilization Top 5

Fee For Service

April 1, 2019 - March 31, 2020

Member Age Band	Age Band Description	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
A	Age <1	LEVETIRACETAM	20	20	678	2,551
A	Age <1	TOPIRAMATE	5	5	130	360
A	Age <1	VIGADRONE	4	4	120	240
A	Age <1	GABAPENTIN	2	2	39	45
A	Age <1	CLOBAZAM	1	1	30	120
B	Age 1-4	LEVETIRACETAM	575	575	17,897	119,106
B	Age 1-4	CLOBAZAM	138	138	4,210	26,361
B	Age 1-4	TOPIRAMATE	117	117	3,880	12,988
B	Age 1-4	EPIDIOLEX	100	100	3,023	6,743
B	Age 1-4	ZONISAMIDE	86	86	2,580	7,200
C	Age 5-9	LEVETIRACETAM	965	965	30,208	319,576
C	Age 5-9	OXCARBAZEPINE	459	459	13,578	99,437
C	Age 5-9	CLOBAZAM	319	319	9,122	59,584
C	Age 5-9	LAMOTRIGINE	284	284	8,643	36,736
C	Age 5-9	VALPROIC ACID	212	212	6,307	74,207
D	Age 10-19	LAMOTRIGINE	2,222	2,222	66,187	134,222.5
D	Age 10-19	OXCARBAZEPINE	1,740	1,740	52,914	189,077.667
D	Age 10-19	LEVETIRACETAM	1,612	1,612	49,010	639,414
D	Age 10-19	TOPIRAMATE	1,054	1,054	31,397	68,073
D	Age 10-19	DIVALPROEX SODIUM DR	667	667	19,643	43,587

N. Psychotropic Medications for Children and Adolescents

Therapeutic Class: Psychotropic Agents
Last Reviewed by the DUR Board: September 3, 2015

Psychotropic medications for children and adolescents are subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for billing information.

Authorization will be given if the following criteria are met and documented.

1. Coverage and Limitations

The DHCFP requires prior authorization approval for children and adolescents for the psychotropic therapeutic classes below and medication combinations considered to be poly-pharmacy. The DHCFP has adopted the following practice standards to strengthen treatment outcomes for our children and adolescents.

a. The psychotropic therapeutic classes subject to this policy are:

1. Antipsychotics

2. Antidepressants

3. Mood Stabilizers (including lithium and anticonvulsants used for behavioral health indications.)

4. Sedative hypnotics

5. Antianxiety agents

b. For all children under 18 years of age, the following must be documented in the medical record for authorization.

1. For psychotropic medications in this age group, when possible, be prescribed by or in consultation with a child psychiatrist.

2. Psychotropic medication must be part of a comprehensive treatment plan that addresses the education, behavioral management, living home environment and psychotherapy.

3. Physician and/or prescriber monitoring is required while the recipient is utilizing any psychotropic medication.

a. For recipients who are in initial treatment (have not received any doses previously) or are continuing therapy but are considered unstable (has had a dose change in the last three months), medical documentation must support a monthly or more frequent visit with the physician and/or precsriber. If the recipient was discharged from

an institution on the medication, the follow-up visit(s) can be with their treating physician and/or prescriber.

b. For recipients who are considered stable in their medication therapy, medical documentation must support visits with the treating physician at least every three months.

c. Poly-pharmacy: Each psychotropic medication prescribed must be independently treating a specific symptom and/or diagnosis.

1. Poly-pharmacy (intra-class) is defined as more than one drug within the same therapeutic class within a 60-day time period.

a. Prior authorization approval is required for two or more drugs in the same therapeutic class within a 60-day period.

2. Poly-pharmacy (inter-class) is defined as more than one drug across different therapeutic classes within a 60-day time period.

a. Prior authorization approval is required for four or more drugs across all psychotropic therapeutic classes listed in this policy within a 60-day time period.

3. Approval for poly-pharmacy may be given in situations where the requested medication(s) will be used for cross tapering and situations where the recipient will be discontinuing the previously prescribed agent. A 30-day cross-taper will be allowed.

4. Approval for poly-pharmacy may be given for a medication to augment the effect of another psychotropic medication as long as the purpose of the poly-pharmacy is clearly documented in the recipient's medical record and each agent is supported by individual authorizations.

5. The recipient must have a trial of each individual medication alone. The reasons for an inadequate response must be documented in the medical record.

6. For intra-class and inter-class poly-pharmacy, all psychotropic medications must be utilized for a medically accepted indication as established by the FDA, and/or peer reviewed literature.

d. For children under six years of age, in addition to the Coverage and Limitation requirements, all psychotropic medications require a prior authorization approval and must be utilized for a medically accepted indication as established by the FDA and/or peer-reviewed literature.

e. Continuity of Care. In an effort to improve recipient safety and quality of care:

1. For recipients under 18 years of age, who have been discharged from an institutional facility, they will be allowed to remain on their discharge medication regimen for up to six months to allow the recipient time to establish outpatient mental health services. The initial prior authorization after discharge must document the name of the discharge institution and the date of discharge.

2. For all other recipients under the age of 18, a six month prior authorization will be granted to cover current medication(s) when it is documented that the recipient has been started and stabilized. This will allow the recipient time to establish services if necessary and to transition to medication(s) per Nevada Medicaid policy.

2. Exceptions to this criteria for Anticonvulsants and ADD/ADHD medications:

a. Treatment for seizure disorders with anticonvulsants are not subject to this policy. The ICD Codes for Epilepsy and/or Convulsions will bypass the prior authorization requirement at the pharmacy POS if the correct ICD Code is written on the prescription and transmitted on the claim. Or the prior authorization requirement will be overridden for anticonvulsant medications when the prescriber has a provider Specialty Code of 126, neurology or 135, pediatric neurology, in the POS system.

b. The current policy for treatment of ADD/ADHD is to be followed. Refer to this Chapter's Appendix A.

3. Prior Authorization Guidelines

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When

combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).

- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri¶¶)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔

Drug	Generic Availability
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon, Depakene)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.
¶¶ FDA-approved product, but not yet marketed.
(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *	✔ *			A		✔, A*	✔, A*		✔ *		✔, A*		A*	✔ *	✔, A*	✔ *
Primary generalized tonic-clonic seizure (grand mal)			✔									✔			✔ *			A*	A*
Absence seizure (petit mal)						✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures									A										
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *			A*	✔, A								A*				A*	
Seizures of Dravet syndrome		✔ *																	
Juvenile myoclonic epilepsy (JME)																			A*
Emergency/acute/short-term use for seizure control (see notes)								✔ *							✔ *				
Akinetic and myoclonic seizures						✔, A													
Convulsive disorders (see notes)								A*											
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																
Migraine prophylaxis									✔ *										
Trigeminal neuralgia			✔ *																
Postherpetic neuralgia																✔ *			
Bipolar disorder			✔ *						✔ *									✔ *	
Panic disorder, with or without agoraphobia						✔													
Anxiety disorder; short-term relief of anxiety symptoms							✔	✔											
Symptomatic relief of acute alcohol withdrawal							✔	✔											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome								A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)													A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✔, A*		✔*		✔*	A*	✔, A*			A*	✔, A*	✔, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✔*		✔, A*				✔, A*			
Absence seizure (petit mal)		✔*												✔, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✔*			✔*			✔*									
Infantile spasms															✔*	
Convulsive disorders (see notes)						✔*										
Migraine prophylaxis													✔*	✔*		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
  - Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure

activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age

- Divalproex sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (≥ 10 years of age for all formulations)
  - Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (≥ 10 years of age for extended-release tablets; age not specified for tablets/sprinkle capsules)
  - The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
    - Treatment of the manic episodes associated with bipolar disorder (tablets)
    - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)
- Eslicarbazepine:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- Ethotoin:
  - Complex partial (psychomotor) seizures
- Everolimus:
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- Felbamate:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- Fosphenytoin:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- Gabapentin:
  - Adjunctive therapy in the treatment of partial-onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- Lacosamide:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- Lamotrigine immediate-release formulations:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- Lamotrigine extended-release tablets:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:
    - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); adjunctive treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg

(tablets for oral suspension [Spritam])
    - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years of age with JME
    - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for the treatment of partial-onset seizures in patients ≥ 12 years of age
- Methsuximide:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- Midazolam nasal spray:
  - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- Oxcarbazepine immediate-release formulations:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- Oxcarbazepine extended-release tablets:
  - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- Pentobarbital:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- Perampanel:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- Phenobarbital (not FDA-approved):
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- Phenytoin oral formulations:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- Phenytoin injection:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- Pregabalin:
  - Adjunctive therapy for treatment of partial-onset seizures in patients ≥ 1 month of age
- Primidone:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- Rufinamide:
  - Adults and pediatric patients ≥ 1 year of age
- Stiripentol:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- Tiagabine:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- Topiramate:
  - Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for

tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:

        - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
        - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
        - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest

probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to

placebo (*Thiele et al 2018*; *Devinsky et al* 2018; *Devinsky et al* 2017). To date, no comparative trials have been published.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following:
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.

        - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
        - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
        - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
    - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
    - Recommendations from the 2004 guideline include the following:
        - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
        - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
        - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
        - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
        - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
    - Recommendations from the 2018 guideline include the following:
        - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
            - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
            - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
            - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
            - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
            - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
        - As monotherapy in patients with TRAFE:
            - Eslicarbazepine use may be considered to decrease seizure frequency.
            - Data are insufficient to recommend use of second- and the other third-generation AEDs.
        - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
        - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
        - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
            - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
            - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
            - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
            - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
        - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.

        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.

- The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
- Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.

- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of "wait and see" is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
      - Dravet syndrome: topiramate, zonisamide, valproate
      - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
      - Provoked or situational seizures: carbamazepine
    - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.

        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)

- neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
- anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
- severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, fosphenytoin, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
- hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
- hepatocellular injury (cannabidiol)
- prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
- serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
- multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
- severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
- hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- Cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
- Abnormal magnetic resonance imaging signals in infants (vigabatrin)
- Intramyelinic edema (vigabatrin)

- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
  - Felbamate:
    - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
    - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
  - Fosphenytoin and phenytoin:
    - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.

- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)¶	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene, Depacon)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available
¶ FDA-approved product, but not yet marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

REFERENCES

- Afinitor Disperz [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Inc.; January 2020.
- Aptiom [package insert], Marlborough, MA: Sunovion Pharmaceuticals Inc.; March 2019.
- Banzel [package insert], Woodcliff Lake, NJ: Eisai Inc.; November 2019.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758-1765.
- Briviact [package insert], Smyrna, GA: UCB Inc.; May 2018.
- Campos MSA, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. *Int J Clin Pharm*. 2018;40(3):589-598. doi: 10.1007/s11096-018-0641-9.

- Carbatrol [package insert], Lexington, MA: Shire US Inc.; August 2018.
- Celontin [package insert], New York, NY: Pfizer Inc.; November 2013.
- Centers for Disease Control and Prevention (CDC). Epilepsy: Types of Seizures. CDC Web Site. https://www.cdc.gov/epilepsy/basics/types-of-seizures.htm. Updated January 17, 2018. Accessed February 25, 2020.
- Cerebyx [package insert], New York, NY: Pfizer Inc.; January 2020.
- Depacon [package insert], North Chicago, IL: AbbVie Inc.; November 2019.
- Depakene [package insert], North Chicago, IL: AbbVie Inc.; September 2019.
- Depakote (tablets) [package insert], North Chicago, IL: AbbVie Inc.; December 2019.
- Depakote ER [package insert], North Chicago, IL: AbbVie Inc.; December 2019.
- Depakote Sprinkle Capsules [package insert], North Chicago, IL: AbbVie Inc.; December 2019.
- Detyniecki K, Van Ess PJ, Sequeira DJ, Wheless JW, Meng TC, Pullman WE. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters-a randomized, double-blind, placebo-controlled trial. *Epilepsia*. 2019;60(9):1797-1808.
- Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med*. 2018;378(20):1888-1897. doi: 10.1056/NEJMoa1714631.
- Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376(21):2011-2020. doi: 10.1056/NEJMoa1611618.
- Diacomit [package insert]. Beauvais, France: Biocodex; August 2018.
- Diastat & Diastat AcuDial [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; December 2016.
- Diazepam (injection) [package insert], Lake Forest, IL: Hospira Inc.; May 2019.
- Diazepam (oral solution) and Diazepam Intensol (oral concentrate) [package insert], Philadelphia, PA: Lannet Company, Inc.; March 2017.
- Dilantin-125 (oral suspension) [package insert], New York, NY: Pfizer Inc.; July 2019.
- Dilantin (capsules) [package insert], New York, NY: Pfizer Inc.; August 2019.
- Dilantin Infatabs (chewable tablets) [package insert], New York, NY: Pfizer Inc.; August 2019.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 20, 2020.
- Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice Parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004; 63:959-965 (guideline retired February 27, 2018).
- Elepsia XR [package insert]. Cranbury, NJ: Sun Pharmaceuticals; December 2019.
- Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; December 2018.
- Epilepsy Foundation. Lennox-Gastaut Syndrome. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. Reviewed February 2020. Accessed February 25, 2020.
- Epilepsy Foundation. Seizure Types. Epilepsy Foundation Web site. https://epilepsychicago.org/epilepsy/seizure-types/generalized-seizures/. 2016. Accessed February 25, 2020.
- Epilepsy Foundation. Types of Epilepsy Syndromes. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes. Reviewed September 2013. Accessed February 25, 2020.
- Equetro [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; October 2016.
- FDA News Release. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Food and Drug Administration website: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm, Accessed February 25, 2020.
- Felbatol [package insert], Somerset, NJ: Meda Pharmaceuticals Inc.; May 2018.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
- Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017(A);58(4):531-542.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017(B);58(4):522-530.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(A);62:1252-1260.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(B);62:1261-1273.
- French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomized, double-blind, placebo-controlled study. *Lancet.* 2016;388(10056):2153-2163. doi: 10.1016/S0140-6736(16)31419-2.
- Fycompa [package insert], Woodcliff Lake, NJ: Eisai Inc.; May 2019.
- Gabitril [package insert], North Wales, PA: Teva Pharmaceuticals USA Inc.; May 2018.
- Glauser T, Ben-Menachem E, Bourgeois B, et al; for the ILAE subcommission of AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551-563.
- Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61.
- Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980 (guideline reaffirmed January 20, 2018).
- Gralise [package insert], Newark, CA: Depomed Inc.; September 2015.
- Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology

Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(A);73:133-141 (guideline reaffirmed July 13, 2013).
- Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(B);73:142-149 (guideline reaffirmed July 13, 2013).
- Hirschfeld RM, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder; second edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Originally published April 2002. Accessed February 25, 2020.
- Hirtz D, Berg A, Bettis D, et al. Practice Parameter: treatment of the child with a first unprovoked seizure. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60:166-175 (guideline reaffirmed October 20, 2018).
- Horizant [package insert], Atlanta, GA: Arbor Pharmaceuticals LLC; October 2016.
- Hu Q, Zhang F, Teng W, et al. Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis. *J Neurol.* 2018;265(1):1-11. doi: 10.1007/s00415-017-8621-x.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018(A);91(2):82-90. doi: 10.1212/WNL.0000000000005756.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2018(B);91(2):74-81. doi: 10.1212/WNL.0000000000005755.
- Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103-2113. doi: 10.1056/NEJMoa1905795.
- Karceski S. Initial treatment of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated May 23, 2019. Accessed February 20, 2020.
- Keppra (injection) [package insert], Smyrna, GA: UCB Inc.; October 2019.
- Keppra (tablets & oral solution) [package insert], Smyrna, GA: UCB Inc.; October 2019.
- Keppra XR [package insert], Smyrna, GA: UCB Inc.; October 2019.
- Klonopin [package insert], South San Francisco, CA: Genentech Inc.; October 2017.
- Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705-1713 (guideline reaffirmed January 20, 2018).
- Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *Lancet Neurol.* 2020;19(1):38-48.
- Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919-926.
- Lamictal (tablets, chewable dispersible tablets & orally disintegrating tablets) [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2018.
- Lamictal XR [package insert], Research Triangle Park, NC: GlaxoSmithKline; September 2019.
- LexiComp Web site. http://online.lexi.com/lco/action/home/switch. Accessed February 25, 2020.
- Lyrica [package insert], New York, NY: Pfizer Inc.; June 2019.
- Lyrica CR [package insert], New York, NY: Pfizer Inc.; June 2019.
- Mysoline [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; October 2019.
- Nayzilam [package insert]. Plymouth, MN: Proximagen LLC; May 2019.
- Nembutal [package insert], Lake Forest, IL: Akorn, Inc.; December 2016.
- Neurontin [package insert], New York, NY: Pfizer Inc.; August 2019.
- Nevitt SJ, Marson AG, Tudur Smith C. Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev*. 2019;18;7:CD001911.
- Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD011412. doi: 10.1002/14651858.CD011412.pub3.
- Onfi [package insert], Deerfield, IL: Lundbeck Inc.; June 2018.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 20, 2020.
- Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache*. 2019;59(8):1144-1157.
- Oxtellar XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; December 2018.
- Peganone [package insert], Lebanon, NJ: Recordati Rare Diseases; July 2016.
- Phenobarbital (elixir) [package insert], Huntsville, AL: Qualitest Pharmaceuticals; December 2018.
- Phenobarbital (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; December 2018.
- Phenobarbital (tablet) [package insert], Eatontown, NJ: Hikma Pharmaceuticals USA Inc.; October 2018.
- Phenytoin (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; November 2017.
- Post RM. Bipolar disorder in adults: choosing maintenance treatment. UpToDate Web site. www.uptodate.com. Updated November 9, 2019. Accessed February 20, 2020.
- Qudexy XR [package insert], Maple Grove, MN: Upsher-Smith Laboratories Inc.; February 2019.
- Rosati A, Ilvento L, Lucenteforte E, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: a network meta-analysis. *Epilepsia.* 2018;59(2):297-314. doi: 10.1111/epi.13981.

- Sabril [package insert], Deerfield, IL: Lundbeck Inc.; February 2020.
- Schachter SC. Overview of the management of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated June 11, 2019. Accessed February 20, 2020.
- Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345 (guideline reaffirmed July 18, 2015).
- Sirven JI. Evaluation and management of drug-resistant epilepsy. UpToDate Web site. www.uptodate.com. Updated December 20, 2018. Accessed February 20, 2020.
- Spritam [package insert], Blue Ash, OH: Aprecia Pharmaceuticals Company; September 2018.
- Stovall J. Acute bipolar mania and hypomania in adults: general principles of pharmacotherapy. UpToDate Web site. www.uptodate.com. Updated December 11, 2018. Accessed February 20, 2020.
- Sympazan [package insert]. Warren, NJ: Aquestive Therapeutics; November 2018.
- Tegretol and Tegretol-XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corp.; March 2018.
- Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3.
- Topamax [package insert], Titusville, NJ: Janssen Pharmaceuticals Inc.; May 2019.
- Tranxene T-TAB [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; May 2018.
- Trileptal [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2019.
- Trokendi XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; February 2019.
- Valium [package insert], South San Francisco, CA: Genentech Inc.; June 2017.
- Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed February 25, 2020.
- Valtoco [package insert], San Diego, CA: Neurelis, Inc.; January 2020.
- Vimpat [package insert], Smyrna, GA: UCB Inc.; June 2019.
- Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015;56(8):1185-1197.
- World Health Organization. Guidelines on neonatal seizures. World Health Organization Web site. http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/. 2011. Accessed February 25, 2020.
- Xcopri [package insert], Paramus, NJ: SK Life Science Inc.; November 2019.
- Zarontin (capsules) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zarontin (oral solution) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zhu LN, Chen D, Xu D, Tan G, Wang HJ, Liu L. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: an indirect comparison. *Seizure*. 2017;51:121-132.
- Zhao T, Feng X, Liu J, et al. Evaluate the efficacy and safety of anti-epileptic medications for partial seizures of epilepsy: A network meta-analysis. *J Cell Biochem*. 2017;118(9):2850-2864. doi: 10.1002/jcb.25936.
- Zonegran [package insert], St. Michael, Barbados: Concordia Pharmaceuticals Inc.; September 2019.

Publication Date: March 19, 2020.

INTRODUCTION

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Simon 2015*).
  - MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. The condition is more prevalent among females and persons aged 40 to 59. From 2009 to 2012, 7.6% of Americans 12 years of age or older had depression (moderate or severe depressive symptoms in the past 2 weeks) (*Pratt and Brody 2014*).
  - Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). The effectiveness of SGAs is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, mirtazapine, and bupropion are considered optimal for the treatment of MDD in most patients (*American Psychiatric Association [APA] 2010, Qaseem et al 2016, Veteran's Affairs/Department of Defense [VA/DoD] 2016*).
    - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (SGA or CBT) or augmenting with a second SGA or psychotherapy is recommended (*Gartlehner et al 2015a, VA/DoD 2016*).
- This review includes SGAs other than those classified as SSRIs. It does not include first-generation antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The focus of this review will be the safety and efficacy of the SNRIs, serotonin modulators, and atypical antidepressants in the treatment of MDD and other psychiatric FDA-approved indications.
  - The SNRIs approved for MDD include Cymbalta (duloxetine), Effexor (venlafaxine), Effexor XR (venlafaxine extended-release), Fetzima (levomilnacipran), Khedezla (desvenlafaxine extended-release), and Pristiq (desvenlafaxine succinate extended-release). They work by blocking presynaptic serotonin and norepinephrine transporter proteins, thereby inhibiting neurotransmitter reuptake (*Nelson 2016*).
    - Savella (milnacipran) is an SNRI approved only for fibromyalgia; therefore, it will not be included in this review. Although duloxetine is approved for other indications (ie, chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia), these indications will not be addressed in this review (*Nelson 2016*).
  - The serotonin modulators include Desyrel (trazodone), Serzone (nefazodone), Trintellix (vortioxetine), and Viibryd (vilazodone). They act as serotonin receptor antagonists and/or agonists and inhibit reuptake of postsynaptic serotonin to varying degrees (*Hirsch and Birnbaum* 2017).
    - Oleptro (trazodone extended-release) was approved in 2010 and discontinued in 2015; thus, it will not be included in this review (*Food and Drug Administration [FDA] 2017*).
  - The atypical antidepressants include bupropion and mirtazapine (*Hirsch and Birnbaum 2016*).
    - Bupropion is a monocyclic aminoketone which inhibits the presynaptic reuptake of dopamine and norepinephrine.
      - Bupropion is available a variety of formulations, including Aplenzin (bupropion hydrobromide), Forfivo XL (bupropion hydrochloride extended-release), Wellbutrin (bupropion hydrochloride), Wellbutrin SR (bupropion hydrochloride sustained-release), and Wellbutrin XL (bupropion hydrochloride extended-release). Zyban (bupropion hydrochloride sustained-release) is only indicated for smoking cessation and will not be discussed in this review.
    - Mirtazapine is a piperazinoazepine compound that acts as a potent antagonist of 5-hydroxytryptamine $(5\text{-HT})_2$, 5-HT_3, and histamine receptors and a moderate antagonist of peripheral α_1-adrenergic and muscarinic receptors.
- Some of the products included in this review have additional psychiatric indications other than MDD, including MDD with a seasonal pattern (formerly known as seasonal affective disorder), generalized anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder.

- MDD with a seasonal pattern is characterized by a regular temporal relationship between particular periods of the year and the onset and remission of depressive symptoms (*APA 2010*).
- GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
- PD is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*APA 2009, Bandelow et al 2012*).
- Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Atypical agents	
Aplenzin (bupropion hydrobromide)	-
Forfivo XL (bupropion hydrochloride extended-release)	-
Remeron (mirtazapine)	✔
Remeron SolTab (mirtazapine ODT)	✔
Wellbutrin (bupropion hydrochloride)	✔
Wellbutrin SR (bupropion hydrochloride sustained-release)	✔
Wellbutrin XL (bupropion hydrochloride extended-release)	✔
SNRIs	
Cymbalta (duloxetine)	✔
Effexor XR (venlafaxine extended-release)	✔
Fetzima (levomilnacipran)	-
Khedezla (desvenlafaxine extended-release)	✔
Pristiq (desvenlafaxine succinate extended-release)	✔
venlafaxine*	✔
Serotonin modulators	
nefazodone*	✔
trazodone*	✔
Trintellix (vortioxetine)	-
Viibryd (vilazodone)	-

* Branded Effexor (venlafaxine), Serzone (nefazodone), and Desyrel (trazodone) are no longer marketed.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA Approved Indications for Atypical Agents

Indication	Aplenzin (bupropion hydrobromide)	Forfivo XL (bupropion hydrochloride extended-release)	Remeron (mirtazapine)	Remeron SolTab (mirtazapine ODT)	Wellbutrin (bupropion hydrochloride)	Wellbutrin SR (bupropion hydrochloride sustained-release)	Wellbutrin XL (bupropion hydrochloride extended-release)
MDD	✔	✔	✔	✔	✔	✔	✔
Prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder	✔						✔

(*Prescribing information: Aplenzin 2017, Forfivo XL 2017, Remeron 2016, Remeron SolTab 2016, Wellbutrin 2017, Wellbutrin SR 2017, Wellbutrin XL 2017*)

Table 3. FDA Approved Indications for SNRIs

Indication	Cymbalta (duloxetine)	Effexor XR (venlafaxine extended-release)	Fetzima (levomilnacipran)	Khedezla (desvenlafaxine extended-release)	Pristiq (desvenlafaxine succinate extended-release)	venlafaxine
MDD	✔	✔	✔	✔	✔	✔
Chronic musculoskeletal pain	✔					
Diabetic peripheral neuropathy	✔					
Fibromyalgia	✔					
GAD	✔	✔				
PD		✔				
Social anxiety disorder		✔				

(*Prescribing information: Cymbalta 2017, Effexor XR 2017, Fetzima 2017, Khedezla 2017, Pristiq 2017, venlafaxine 2016*)

Table 4. FDA Approved Indications for Serotonin Modulators

Indication	nefazodone	trazodone	Trintellix (vortioxetine)	Viibryd (vilazodone)
MDD	✔	✔	✔	✔

(*Prescribing information: nefazodone 2015, trazodone 2016, Trintellix 2017, Viibryd 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

MDD

- Although there is conflicting evidence, most meta-analyses and systematic reviews conclude that the SNRIs, serotonin modulators, and atypical antidepressants have comparable efficacy to SSRIs and to one another in the treatment of MDD. No robust or replicated results have established a clinically meaningful difference in efficacy among classes or within a class (*Simon 2015*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).
  - Results from direct and indirect comparisons based on 61 head-to-head trials and 31 placebo-controlled (PC) trials did not detect any substantial differences in efficacy among the SGAs for MDD (moderate strength of evidence).
  - While the overall adverse event (AE) profiles and rates of discontinuation are similar among SGAs, the incidence of specific AEs varies among agents (high strength of evidence).
    - Venlafaxine was associated with higher rates of nausea and vomiting than SSRIs based on a meta-analysis of 15 studies (high strength of evidence).
    - Mirtazapine was associated with higher weight gain than citalopram, fluoxetine, paroxetine, and sertraline based on results from 7 trials (high strength of evidence).
    - Sertraline was associated with a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine based on results of 15 studies (moderate strength of evidence).
    - Trazodone was associated with a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine based on results from 6 trials (moderate strength of evidence).
    - Bupropion was associated with lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline based on results from 6 trials (high strength of evidence).
  - Results from 7 trials suggest that mirtazapine has a significantly faster onset of action compared to citalopram, fluoxetine, paroxetine, and sertraline (moderate strength of evidence).
  - Separate meta-analyses of the available head-to-head trials also suggested comparable efficacy between SGAs. The clinical significance of the marginal but statistically significant differences reflected in certain head-to-head comparisons remains to be determined.
    - A meta-analysis of 6 studies (n = 1197) directly comparing venlafaxine to fluoxetine demonstrated a significantly higher odds ratio [OR] of response (defined as ≥ 50% reduction of symptoms from baseline) with venlafaxine (OR 1.47; 95% confidence interval [CI], 1.16 to 1.86).
    - A meta-analysis of 3 studies (n = 470) directly comparing sertraline to venlafaxine demonstrated similar rates of response (OR 1.18; 95% CI, 0.81 to 1.72).
    - A meta-analysis of 3 studies (n = 849) directly comparing paroxetine to duloxetine also demonstrated similar rates of response (OR 0.84; 95% CI, 0.63 to 1.12).
- The newer SGAs, levomilnacipran, vilazodone, and vortioxetine, were not included in the 2011 AHRQ review but were included in the 2015 AHRQ comparative effectiveness review which evaluated SGAs and nonpharmacological treatments for adult patients with MDD. The available evidence did not warrant the selection of one SGA over another based on efficacy in initial therapy, switching SGAs, or augmenting SGAs for MDD (*Gartlehner et al 2015a*).
  - Two direct comparisons (n = 1123) with patients who did not achieve remission following an initial adequate SGA trial and were switched to another SGA did not demonstrate a substantial differences in response rates between SGAs (moderate strength of evidence). Additionally, results from one of those studies (n = 727) did not demonstrate a substantial difference between the SGAs in remission rates, decrease in severity of depression, overall risk of AEs, or suicidal ideas or behaviors (low strength of evidence).
  - One direct comparison (n = 565) with patients who did not achieve remission following an initial adequate SGA trial and were treated with add-on therapy with another SGA did not demonstrate substantial differences in the rates of response or remission between SGAs (low strength of evidence).
- In a Cochrane review of 15 studies (n = 7746) with vortioxetine for MDD, patients on vortioxetine were more likely to respond to therapy than those on placebo (Mantel-Haenszel risk ratio [RR] 1.35; 95% CI, 1.22 to 1.49; 14 studies, 6220 participants) with a low quality of evidence. The response rate for vortioxetine was comparable to that of SNRIs as a class (RR 0.91; 95% CI, 0.82 to 1.00; 3159 participants) but lower compared with duloxetine alone (RR 0.86; 95% CI,

0.79 to 0.94; 6 studies, 2392 participants), with a very low quality of evidence. The clinical implications of these results are unclear (*Koesters et al 2017*).

- A multiple-treatments meta-analysis of 117 randomized controlled trials (RCTs) (n = 25,928) found clinically important differences when comparing bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine (not approved in the United States), sertraline, and venlafaxine for the acute treatment of adults with MDD. Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious antidepressants, while escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants (*Cipriani et al 2009*).
  - Patients on mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more likely to respond to therapy than those on duloxetine (OR 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (OR 1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (OR 1.41, 1.35, 1.30, and 1.27, respectively), and paroxetine (OR 1.35, 1.30, 1.27, and 1.22, respectively).

MDD with a Seasonal Pattern: extended-release bupropion

- A Cochrane review of 3 RCTs (n = 1100) evaluated SGAs for the prevention of seasonal affective disorder in adults. Extended-release bupropion was shown to be an effective intervention compared to placebo (RR 0.56; 95% CI, 0.44 to 0.72) for the prevention of depressive episodes in patients with MDD with a seasonal pattern, with a moderate quality of evidence. Bupropion therapy was also associated with a greater incidence of headaches, insomnia, and nausea compared to placebo. There was insufficient evidence to compare bupropion to other SGAs or to other interventions such as light therapy, psychotherapy, or melatonin (*Gartlehner et al 2015b*).

GAD: duloxetine and extended-release venlafaxine

- A non-inferiority RCT (n = 984) randomized adults with GAD to receive duloxetine, extended-release venlafaxine, or placebo. The primary outcome of response to therapy was defined as ≥ 50% reduction from baseline in Hamilton Anxiety Rating Scale (HAMA) total score. Response rates for duloxetine, extended-release venlafaxine, and placebo were 56%, 58%, and 40%, respectively. Duloxetine and extended-release venlafaxine both demonstrated superiority over placebo ($p \leq 0.001$ for both). The authors concluded that duloxetine met all statistical and clinical criteria for non-inferiority and exhibited a similar tolerability profile compared to extended-release venlafaxine for the treatment of adults with GAD (*Allgulander et al 2008*).

PD: extended-release venlafaxine

- A Cochrane review of 35 double-blind RCTs (n = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with PD. An analysis of 2 studies (n = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for PD (RR 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; $I^2 = 1\%$; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for PD (RR 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
- In a meta-analysis of 50 studies (n = 5236) of antidepressants for PD, the following antidepressants demonstrated superiority over placebo in the reduction from baseline of overall anxiety symptoms (in increasing order of effectiveness): citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

Social Anxiety Disorder: extended-release venlafaxine

- A systematic review and meta-analysis of 51 RCTs (n = 9914) evaluated pharmacotherapies for social anxiety disorder. Venlafaxine demonstrated a superior response rate, assessed by the Clinical Global Impressions Improvement (CGI-I) scale, vs. placebo (RR 1.59; 95% CI, 1.38 to 1.83; 4 studies; 1173 participants) (*Ipser et al 2008*).
- Another systematic review and meta-analysis of 3 head-to-head trials and 15 PC trials did not reveal significant differences in the efficacy of SGAs for social anxiety disorder. Pooled evidence from PC trials supported the superiority over placebo in the CGI-I response of escitalopram (relative benefit [RB] 1.3; 95% CI, 1.2 to 1.5), paroxetine (RB 1.9; 95% CI, 1.5 to 2.3), sertraline (RB 1.8; 95% CI, 1.5 to 2.2), and venlafaxine (RB 1.7; 95% CI, 1.5 to 1.9) for social anxiety disorder. While the network meta-analysis did not find significant differences in efficacy among the SGAs, there were differences in the AE profiles (*Hansen et al 2008*).

CLINICAL GUIDELINES

MDD

- **Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of MDD** (*2016*)
  - As first-line treatment for uncomplicated mild to moderate MDD, evidence-based psychotherapy or evidence-based pharmacotherapy should be offered. Selection should be based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication, and provider training/competence.
    - Evidence-based pharmacotherapy includes SSRIs (except fluvoxamine), SNRIs, mirtazapine, and bupropion.
    - The evidence does not support recommending a specific psychotherapy or pharmacotherapy over another.
    - In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy is recommended.
  - In cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant did not achieve a response or remission. In patients who have demonstrated a partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.
- **Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With MDD: A Clinical Practice Guideline From the American College of Physicians (ACP)** (*Qaseem et al 2016*)
  - Clinicians are recommended to select between either CBT or SGAs to treat patients with MDD after discussing treatment effects, AE profiles, cost, accessibility, and preferences with the patient (Grade: Strong recommendation, moderate-quality evidence).
  - There are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) AEs. Bupropion is associated with a lower rate of sexual AEs than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss AE profiles before selecting a medication.
- **American Psychiatric Association (APA) Practice Guideline for the Treatment of MDD: 3rd Edition** (*2010*)
  - The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference.
  - For most patients, an SSRI, an SNRI, mirtazapine, or bupropion is optimal.
  - In general, the use of nonselective MAOIs (eg, phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments.

MDD with a Seasonal Pattern

- Light therapy may be suggested for adult patients with mild to moderate MDD with a seasonal pattern. While there is limited evidence supporting the effectiveness of light therapy, the benefits outweigh the risks. For severe seasonal MDD, pharmacological intervention with an antidepressant is recommended, and light therapy may be considered as adjunctive therapy. Extended-release bupropion is FDA approved for use in patients with MDD with seasonal pattern (*APA 2010, VA/DoD 2016*).

GAD

- According to the World Federation of Societies of Biological Psychiatry (WFSBP), the first-line pharmacologic therapies for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed (*Bandelow et al 2012*).

PD

- The WFSBP recommends SSRIs or venlafaxine as first-line pharmacotherapies for PD. For severe acute panic attacks, short-acting benzodiazepines may be needed. Treatment should continue for at least several months after remission in order to prevent relapses (*Bandelow et al 2012*).
- For the initial treatment of PD, the use of an SSRI, SNRI, TCA, benzodiazepine (appropriate as monotherapy only in the absence of a co-occurring mood disorder), or CBT is strongly supported by evidence of efficacy in numerous RCTs.

There is insufficient evidence to recommend any of the pharmacological or psychosocial interventions as superior to the others, or to routinely recommend a combination of therapies over monotherapy (*APA 2009*).

Social Anxiety Disorder

- The WFSBP recommends SSRIs and venlafaxine for first-line pharmacologic therapy for social anxiety disorder. There is insufficient evidence to recommend benzodiazepines or TCAs. Exposure therapy and CBT are also effective psychotherapies (*Bandelow et al 2012*).

SAFETY SUMMARY

Contraindications

- In general, antidepressants are contraindicated in patients with concurrent administration of MAOIs (trazodone and nefazodone have this listed as a warning rather than a contraindication). The risk for serotonin syndrome is increased with the use of MAOIs, including linezolid and intravenous methylene blue.
- Bupropion products are additionally contraindicated in the following: seizure disorder; current or prior diagnosis of bulimia or anorexia; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs.
- Nefazodone is additionally contraindicated in patients who were withdrawn from nefazodone due to liver injury and in patients concurrently on terfenadine, astemizole, cisapride, pimozide, carbamazepine, or triazolam.

Warnings

- All antidepressants carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking antidepressants.
- Nefazodone labeling also contains a boxed warning for life-threatening hepatic failure and recommends that prescribers consider the risk of hepatic failure associated with nefazodone treatment when deciding among the various treatment options available for MDD. In many cases, this would lead to the conclusion that other drugs should be tried first.
- Neonates exposed to SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with venlafaxine tablets during the third trimester, the potential risks and benefits of treatment should be carefully considered.

AEs

- Common AEs with the antidepressants included in this review are outlined in Table 5 below.

Table 5. AEs of antidepressant medications

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Atypical agents								
Bupropion	0	0	2+ (IR) 1+ (SR)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
SNRIs†,‡								

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects. Refer to topic on acquired long QT syndrome.

† All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Desvenlafaxine§	0	0	1+	0	0	2+	unknown	1+
Duloxetine	0	0	1+	0	0	2+	0-1+	1+
Levomilnacipran§	0**	0	0-1+	0-1+	0	2+†	0	1+
Venlafaxine§	0	1+	1+	0	1+	2+	0-1+	3+
Serotonin modulators								
Nefazodone††	1+	2+	0	1+	0	2+	0	0
Trazodone‡‡	0	4+	0	3+	2+	3+	1+	1+§§
Vilazodone	0	0	2+	0	0	4+***	0	2+
Vortioxetine	0	0	0	0	0	3+	0	1+

Abbreviations: IR = immediate release; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release.
Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

‡ None of the SNRIs have anticholinergic activity. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic effects on the autonomic nervous system) such as dry mouth and constipation, and should be used with caution in narrow angle glaucoma. In addition, levomilnacipran is associated with urinary hesitancy.
§ May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.
** Levomilnacipran has dose dependent effects on urinary hesitancy.
†† Caution: can cause liver failure. Not available in Europe, Canada, and several other countries.
‡‡ Side effect scale is displayed for the antidepressant dose of trazodone.
§§ Trazodone is associated rarely with priapism, which is considered a medical emergency.
*** Vilazodone is associated with higher rates of nausea, vomiting, and diarrhea.

(*Hirsch and Birnbaum 2017, Nelson 2016*)

DOSING AND ADMINISTRATION

- In general, the dose of antidepressants should be gradually reduced prior to complete discontinuation to avoid withdrawal.

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atypical agents				
Aplenzin (bupropion hydrobromide)	Extended-release tablets	Oral	Daily	Increase dose gradually to reduce seizure risk. Dose adjustments may be required in renal or hepatic impairment.
Forfivo XL (bupropion hydrochloride)	Extended-release tablets	Oral	Daily	Not recommended in patients with renal or hepatic impairment due to higher dose. Bupropion treatment should not be initiated with Forfivo XL. Another bupropion formulation should be used for initial dose titration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Remeron (mirtazapine)	Tablets	Oral	Daily	Administered in the evening prior to sleep. Caution is advised in renal or hepatic insufficiency.
Remeron SolTab (mirtazapine)	Orally-disintegrating tablets	Oral	Daily	
Wellbutrin (bupropion hydrochloride)	Tablets	Oral	3 times daily	Dose adjustments may be required in renal or hepatic impairment.
Wellbutrin SR (bupropion hydrochloride)	Sustained-release tablets	Oral	Twice daily	
Wellbutrin XL (bupropion hydrochloride)	Extended-release tablets	Oral	Daily	
SNRIs				
Cymbalta (duloxetine)	Delayed-release capsules	Oral	Daily or twice daily	
Effexor XR (venlafaxine)	Extended-release capsules	Oral	Daily	Take with food. Dose adjustments may be required in renal or hepatic impairment.
Fetzima (levomilnacipran)	Extended-release capsules	Oral	Daily	Adjust dose in moderate or severe renal impairment.
Khedezla (desvenlafaxine)	Extended-release tablets	Oral	Daily	Dose adjustments may be required in renal or hepatic impairment. Increased risk of orthostatic hypotension for patients ≥ 65 years.
Pristiq (desvenlafaxine succinate)	Extended-release tablets	Oral	Daily	
venlafaxine*	Tablets	Oral	2 or 3 times daily	Take with food. Dose adjustments may be required in renal or hepatic impairment.
Serotonin modulators				
nefazodone*	Tablets	Oral	Twice daily	Not recommended in active liver disease or elevated baseline serum transaminases.
trazodone*	Tablets	Oral	3 times daily	Take shortly after a meal or light snack. Caution is advised in renal or hepatic impairment.
Trintellix (vortioxetine)	Tablets	Oral	Daily	
Viibryd (vilazodone)	Tablets	Oral	Daily	Take with food.

See the current prescribing information for full details

CONCLUSION

- Despite conflicting evidence, most meta-analyses and systematic reviews conclude that the SNRIs, serotonin modulators, and atypical antidepressants have comparable efficacy to SSRIs and to one another in the treatment of MDD. No robust or replicated results have established a clinically meaningful difference in efficacy among classes of SGAs or within a class (*Simon 2015*).
- While the AE profiles and discontinuation rates are similar among SGAs, the incidence of specific AEs varies among agents (*Gartlehner et al 2011*). Therefore, the overall safety is comparable between the SNRIs, serotonin modulators, and atypical antidepressants, with the exception of nefazodone, which carries a boxed warning for life-threatening hepatic failure.

- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The effectiveness is generally comparable between classes and within classes of SGAs. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*APA 2010, Qaseem et al 2016, VA/DoD 2016*).
  - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. For patients with an insufficient response to initial SGA monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another SGA, augmenting with a second SGA, or augmenting with CBT are all reasonable options (*Gartlehner et al 2015a, VA/DoD 2016*).

REFERENCES

- Allgulander C, Nutt D, Detke M, et al. A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. *J Psychopharmacol*. 2008;22(4):417-25. doi: 10.1177/0269881108091588.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. November 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 1, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition. January 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf. Accessed July 1, 2017.
- Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol*. 2013;28(1):33-45. doi: 10.1097/YIC.0b013e32835a5d2e.
- Aplenzin [package insert], Bridgewater, NJ: Valeant Pharmaceuticals North America LLC.; May 2017.
- Bandelow B, Sher L, Bunevicius R,et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi: 10.3109/13651501.2012.667114.
- Bighelli I, Trespidi C, Castellazzi M, et al. Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database Syst Rev*. 2016;9:CD011567. doi: 10.1002/14651858.CD011567.pub2.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-58. doi: 10.1016/S0140-6736(09)60046-5.
- Cymbalta [package insert], Indianapolis, IN: Lilly USA, LLC; January 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 1, 2017.
- Effexor XR [package insert], Philadelphia, PA: Wyeth Pharmaceuticals Inc.; March 2017.
- Fetzima [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Food and Drug Administration. Determination that Tensilon and Tensilon Preservative Free (edrophonium chloride) injectable and other drug products were not withdrawn from sale for reasons of safety or effectiveness. *Federal Register.* 2015;80(210):66911.
- Forfivo XL [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; May 2017.
- Gartlehner G, Gaynes BN, Amick HR, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder. Agency for Healthcare Research and Quality (AHRQ) Web site. December 2015a. http://www.effectivehealthcare.ahrq.gov/ehc/products/568/2155/major-depressive-disorder-report-151202.pdf. Accessed July 1, 2017.
- Gartlehner G, Hansen RA, Morgan LC, et al. Second-generation antidepressants in the pharmacologic treatment of adult depression: an update of the 2007 comparative effectiveness review. Agency for Healthcare Research and Quality (AHRQ) Web site. December 2011. https://effectivehealthcare.ahrq.gov/ehc/products/210/863/CER46_Antidepressants-update_20111206.pdf. Accessed July 1, 2017.
- Gartlehner G, Nussbaumer B, Gaynes BN,et al. Second-generation antidepressants for preventing seasonal affective disorder in adults. *Cochrane Database Syst Rev*. 2015b;11:CD011268. doi: 10.1002/14651858.CD011268.pub2.
- Hansen RA, Gaynes BN, Gartlehner G, et al. Efficacy and tolerability of second-generation antidepressants in social anxiety disorder. *Int Clin Psychopharmacol*. 2008;23(3):170-9. doi: 10.1097/YIC.0b013e3282f4224a.
- Hirsch M, Birnbaum RJ. Atypical antidepressants: Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated September 14, 2016. Accessed July 1, 2017.
- Hirsch M, Birnbaum RJ. Serotonin modulators: Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated June 12, 2017. Accessed July 1, 2017.
- Ipser JC, Kariuki CM, Stein DJ. Pharmacotherapy for social anxiety disorder: a systematic review. *Expert Rev Neurother*. 2008;8(2):235-57. doi: 10.1586/14737175.8.2.235.
- Khedezla [package insert], Marietta, GA: Osmotica Pharmaceutical US LLC; January 2017.
- Koesters M, Ostuzzi G, Guaiana G, Breilmann J, Barbui C. Vortioxetine for depression in adults. *Cochrane Database Syst Rev*. 2017;7:CD011520. doi: 10.1002/14651858.CD011520.pub2.
- Nefazodone [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2015.
- Nelson C. Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated April 4, 2016. Accessed July 1, 2017.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 1, 2017.
- Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. Nations Center for Health Statistics (NCHS) data brief, no 172. 2014. https://www.cdc.gov/nchs/data/databriefs/db172.htm. Accessed July 1, 2017.
- Pristiq [package insert], Philadelphia, PA: Wyeth Pharmaceuticals Inc.; January 2017.

- Qaseem A, Barry MJ, Kansagara D, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;164(5):350-9. doi: 10.7326/M15-2570.
- Remeron [package insert], Whitehouse Station, NJ: Merck and Co, Inc.; July 2016.
- Remeron SolTab [package insert], Whitehouse Station, NJ: Merck and Co, Inc.; July 2016.
- Simon G. Unipolar major depression in adults: Choosing initial treatment. UpToDate Web site. www.uptodate.com. Updated December 23, 2015. Accessed July 1, 2017.
- Trazodone [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2016.
- Trintellix [package insert], Deerfield, IL: Takeda Pharmaceuticals America, Inc.; April 2017.
- Venlafaxine [package insert], Dayton, NJ: Aurobindo Pharma USA, Inc.; October 2017.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines for the management of major depressive disorder. Department of Veterans Affairs Web site. April 2016. https://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed July 1, 2017.
- Viibryd [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Wellbutrin [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.
- Wellbutrin SR [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.
- Wellbutrin XL [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2017.

Publication Date: August 1, 2017

Therapeutic Class Overview
Antidepressants, SSRI

INTRODUCTION

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Simon 2015*).
  - MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. The condition is more prevalent among females and persons aged 40 to 59. From 2009 to 2012, 7.6% of Americans 12 years of age or older had depression (moderate or severe symptoms in the past 2 weeks) (*Pratt and Brody 2014*).
  - Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). The effectiveness of SGAs is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, mirtazapine, and bupropion are considered optimal for the treatment of MDD in most patients (*American Psychiatric Association [APA] 2010, Qaseem et al 2016, Veteran's Affairs/Department of Defense [VA/DoD] 2016*).
- SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy. This initial action may cause subsequent changes involved in treating depression. SSRIs are selective in that they have relatively little affinity for other types of receptors. Reuptake inhibition occurs soon after SSRIs are started, and the full therapeutic effects of SSRIs may not appear for 3 to 8 (or more) weeks after treatment has started (*Hirsch and Birnbaum 2017*).
- Some of the SSRIs are also used to treat other psychiatric disorders besides MDD, including panic disorder, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social anxiety disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder(PMDD)/premenstrual syndrome (PMS), and bulimia nervosa.
  - GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
  - OCD is characterized by recurrent intrusive thoughts, images, or urges (obsessions) that typically cause anxiety or distress, and by repetitive mental or behavioral acts (compulsions) that the individual feels driven to perform, either in response to an obsession or according to rules that he or she believes must be applied rigidly *(Simpson 2016)*.
  - Panic disorder is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*APA 2009, Bandelow et al 2012*).
  - PMS is characterized by the presence of both physical and behavioral (including affective) symptoms that occur repetitively in the second half of the menstrual cycle and interfere with some aspects of the woman's life. The APA defines PMDD as a severe form of PMS in which symptoms of anger, irritability, and internal tension are prominent *(Yonkers and Casper 2016).*
  - PTSD is a clinically-significant condition with symptoms that have persisted for more than 1 month after exposure to a traumatic event and caused significant distress or impairment in social, occupational, or other important areas of functioning. PTSD can appear alone as the only diagnosis, or more commonly, with another co-occurring disorder, such as a substance use disorder or mood disorder *(Veterans Affairs [VA]/Department of Defense [DoD] 2017)*.
  - Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).
  - Bulimia nervosa is characterized by recurrent episodes of binge eating and inappropriate compensatory behaviors, as well as frequent comorbid psychopathology *(Engel et al 2017)*.
- The scope of this review will be the safety and efficacy of the SSRIs in the treatment of MDD and other psychiatric Food and Drug Administration (FDA)-approved indications. The SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.
  - Brisdelle, a low dose (7.5 mg) paroxetine mesylate formulation, is only FDA-approved for the treatment of moderate to vasomotor symptoms (VMS) associated with menopause. This indication will not be addressed in this review.
- Medispan Therapeutic Class: Selective Serotonin Reuptake Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Brisdelle (paroxetine mesylate) capsules	✔
Celexa (citalopram) oral solution, tablets*	✔
fluoxetine delayed-release (DR) capsules‡	✔
fluoxetine tablets‡	✔
fluvoxamine tablets‡	✔
fluvoxamine ER capsules‡	✔
Lexapro (escitalopram) oral solution, tablets*	✔
Paxil (paroxetine hydrochloride) oral suspension, tablets	✔ †
Paxil CR (paroxetine hydrochloride ER) tablets	✔
Pexeva (paroxetine mesylate) tablets	--
Prozac (fluoxetine) capsules, oral solution*	✔
Sarafem (fluoxetine) capsules‡, tablets	✔
Zoloft (sertraline) oral solution, tablets	✔

*Brand Celexa, Lexapro, and Prozac oral solution are no longer marketed.
†Paxil oral suspension does not have a generic available.
‡Brand Luvox (fluvoxamine) tablets/capsules, Prozac Weekly (fluoxetine) capsules, Prozac (fluoxetine) tablets, and Sarafem (fluoxetine) capsules are no longer marketed.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA Approved Indications for SSRIs

Indication	Citalopram	Escitalopram	Fluoxetine	Fluoxetine (Sarafem)	Fluoxetine DR	Fluvoxamine	Fluvoxamine ER	Paroxetine hydrochloride	Paroxetine hydrochloride ER	Paroxetine mesylate (Brisdelle)	Paroxetine mesylate (Pexeva)	Sertraline
GAD		✔						✔			✔	
MDD	✔	✔	✔		✔			✔	✔		✔	✔
OCD			✔			✔	✔	✔			✔	✔
Moderate to VMS associated with menopause										✔		
Panic disorder			✔					✔	✔		✔	✔
PMDD				✔					✔			✔
PTSD								✔				✔
Social anxiety disorder								✔	✔			✔
Bulimia nervosa			✔									

(*Prescribing information: Brisdelle 2017, Celexa tablets 2017, citalopram oral solution 2017, fluoxetine delayed-release 2015, fluoxetine tablets 2016, fluvoxamine 2017, fluvoxamine extended-release 2015, Lexapro 2017, Paxil 2016, Paxil CR 2016, Pexeva 2017; Prozac 2017, Sarafem 2017, Zoloft 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

GAD

- There is a lack of data available directly comparing different serotonergic reuptake inhibitors (including SSRIs vs SNRIs) for GAD. Trials have generally shown that all serotonergic reuptake inhibitors studied have the same degree of effectiveness, ie, response rates of approximately 60 to 70% for the serotonergic reuptake inhibitors vs. 40% for the placebo. SSRIs that have been shown in randomized control trials (RCTs) to be efficacious for GAD include paroxetine, sertraline, citalopram, and escitalopram. Uncontrolled trials and our clinical experience suggest other SSRIs (eg, fluoxetine and fluvoxamine) are effective for GAD as well (*Bystritsky 2016*).

MDD

- A large body of literature supports the superiority of SSRIs compared with placebo in the treatment of MDD. Although a few analyses suggest small advantages of SNRIs over SSRIs in rates of remission, a preponderance of the data finds no significant evidence of the superiority of any other class or agents over SSRIs. Most individual trials and meta-analyses show no differences in efficacy among individual SSRIs (*APA 2010, VA/DoD 2016*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).

- Overall, treatment effects were similar among SGAs. Some analyses yielded statistically significant differences among treatments, but the magnitudes of differences were modest and probably not clinically relevant.
  - Meta-analyses of head-to-head trials showed statistically significantly greater response rates for escitalopram than citalopram (1 unpublished study and 5 published studies involving 1802 patients) (odds ratio [OR], 1.49, 95% confidence interval [CI], 1.07 to 2.01), and sertraline than fluoxetine (4 studies involving 960 patients) (OR, 1.42, 95% CI, 1.08 to 1.85).
- In several head-to-head trials, overall efficacy in maintaining remission did not significantly differ between escitalopram and desvenlaxafine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine.
- For patients with MDD and accompanying anxiety, 4 head-to-head trials suggested that antidepressants have similar antidepressive efficacy. Two of these studies compared SSRIs (fluoxetine, paroxetine, and sertraline).
- Overall, SGAs caused similar adverse events (AEs); however, the frequency of specific events differed among some drugs. In addition, Discontinuation rates were similar between SSRIs and other SGAs (range of means, 15% to 25%).

- A multiple-treatments meta-analysis of 117 RCTs (n = 25,928) found clinically important differences when comparing bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine (not approved in the United States), sertraline, and venlafaxine for the acute treatment of adults with MDD. (*Cipriani et al 2009*).
  - Patients on mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more likely to respond to therapy than those on duloxetine (OR 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (OR 1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (OR 1.41, 1.35, 1.30, and 1.27, respectively), and paroxetine (OR 1.35, 1.30, 1.27, and 1.22, respectively).
  - Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, and venlafaxine.

OCD

- A Cochrane review of 17 RCT and quasi RCT studies (n = 3097) evaluated the efficacy and AEs of SSRIs vs placebo for OCD in adults. SSRIs as a group were more effective than placebo in reducing the symptoms of OCD between 6 and 13 weeks post-treatment, measured using the Yale-Brown Obsessive Compulsive Scale (YBOCS) (weighted mean difference [WMD] -3.21, 95% CI -3.84 to -2.57). The WMD for individual SSRI drugs were similar and not statistically different. Based on 13 studies (2697 participants), SSRIs were more effective than placebo in achieving clinical response at post-treatment (relative risk [RR] 1.84, 95% CI 1.56 to 2.17). The pooled RR was shown to be similar between individual SSRI drugs. Although reported AEs data were more limited, with few exceptions, the overall and individual AEs for the different SSRIs were always worse than for placebo and, in the majority of cases, the difference was statistically significant. Nausea, headache and insomnia were always reported amongst the most common AEs in clinical trials for each of the drugs (*Soomro et al 2008*).

Panic Disorder

- A Cochrane review of 35 RCTs (n = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with panic disorder. An analysis of 2 studies (n = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for panic disorder (RR 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; I^2 = 1%; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for panic disorder (RR 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
- In a meta-analysis of 50 studies (n = 5236) of antidepressants for panic disorder, the following antidepressants demonstrated superiority over placebo in the reduction from baseline of overall anxiety symptoms (in increasing order of effectiveness): citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

PMDD

- A Cochrane review of 31 RCTs (n = 6785) evaluated the effectiveness and safety of SSRIs for treating PMS. The review compared fluoxetine, paroxetine, sertraline, escitalopram and citalopram vs. placebo. SSRIs reduced overall self-rated symptoms significantly more effectively than placebo. The effect size was moderate when studies reporting end scores were pooled (for moderate dose SSRIs: SMD -0.65, 95% CI -0.46 to -0.84; n = 9 studies, 1276 women; moderate heterogeneity I^2 = 58%; low quality evidence). SSRIs were effective for symptom relief whether taken only in the luteal

phase or continuously, with no clear evidence of a difference in effectiveness between these modes of administration. However, few studies directly compared luteal and continuous regimens and more evidence is needed on this question. Withdrawals due to AEs were significantly more likely to occur in the SSRI group. In secondary analyses, SSRIs were effective for treating specific types of symptoms (eg, psychological, physical and functional symptoms, and irritability) (*Marjoribanks et al 2013*).

PTSD

- A systematic review and meta-analysis of RCTs (n = 51 studies) evaluated the efficacy of all types of pharmacotherapy, as monotherapy, in reducing symptoms of PTSD. SSRIs were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardized mean difference -0.23, 95% CI -0.33 to -0.12). Three drugs were significantly superior to placebo on either clinician- and self-rated PTSD symptom severity combined (paroxetine) or clinician-rated PTSD symptom severity alone (fluoxetine and venlafaxine). Insufficient evidence was found to support the preferential use of individual agents in either combat-related or non-combat-related trauma (*Hoskins et al 2015*).

Social Anxiety Disorder

- A systematic review and meta-analysis of RCTs (41 studies) aimed to identify optimal treatments for social phobia (ie, social anxiety disorder) (*Canton et al 2012*).
  - SSRIs were the most extensively tested in patients with social phobia, with 17 placebo-controlled acute treatment RCTs reported. Almost half of the studies studied paroxetine, with 2 to 3 studies each for escitalopram, fluoxetine, fluvoxamine, and sertraline. The pooled OR for response to each SSRI ranged between 1.98 (95% CI, 1.07 to 3.67) for fluoxetine and 3.41 (95% CI, 2.51 to 4.69) for paroxetine. The overall OR was 2.73 (95% CI, 1.67 to 4.48). With 1 exception, SSRIs had significantly greater Clinical Global Impressions (CGI) response rates compared with placebo.
  - In general, SSRIs showed separation from placebo by weeks 4 to 6 on a number of response or other outcome measures; however SSRI-placebo differences tended to increase out to 12 weeks of treatment.
  - There have been 4 studies assessing the effect of continuation treatment with SSRIs in patients who have responded to acute treatment. In these relapse prevention studies, patients were randomized to remain on their SSRI or were switched to placebo, under double-blind conditions. All 4 studies showed robust effects of the SSRIs in preventing relapse of social phobia (pooled OR 0.25, 95% CI, 0.18 to 0.35).

CLINICAL GUIDELINES

GAD

- **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012)*
  - The first-line pharmacologic therapies for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed.

MDD

- **VA/DoD Clinical Practice Guideline for the Management of MDD** *(VA/DoD 2016)*
  - As first-line treatment for uncomplicated mild to moderate MDD, evidence-based psychotherapy or evidence-based pharmacotherapy should be offered. Selection should be based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication, and provider training/competence.
    - Evidence-based pharmacotherapy includes SSRIs (except fluvoxamine), SNRIs, mirtazapine, and bupropion.
    - The evidence does not support recommending a specific psychotherapy or pharmacotherapy over another.
    - In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy is recommended.
  - In cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant did not achieve a response or remission. In patients who have demonstrated a partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.

- **Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With MDD: A Clinical Practice Guideline From the American College of Physicians (ACP)** (*Qaseem et al 2016*)
  - Clinicians are recommended to select between either cognitive behavioral therapy or SGAs (SSRIs, SNRIs) to treat patients with MDD after discussing treatment effects, AE profiles, cost, accessibility, and preferences with the patient (Grade: Strong recommendation, moderate-quality evidence).
  - There are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) AEs. Bupropion is associated with a lower rate of sexual AEs than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss AE profiles before selecting a medication.
- **American Psychiatric Association (APA) Practice Guideline for the Treatment of MDD: 3rd Edition** (*APA 2010*)
  - The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference.
  - For most patients, an SSRI, an SNRI, mirtazapine, or bupropion is optimal. In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

OCD

- **APA Practice Guideline for the Treatment of OCD** *(APA 2013)*
  - The guideline recommends CBT or a serotonin reuptake inhibitor (ie, SSRIs or clomipramine) as first-line treatments for OCD. Choice of treatment modality depends on many factors, including the nature and severity of the patient's symptoms, the nature of any co-occurring psychiatric and medical conditions and their treatments, the availability of CBT, and the patient's past treatment history, current medications, and preferences.
  - The guideline notes that all SSRIs appear to be equally effective in treating OCD, even though citalopram and escitalopram are not FDA-approved for this indication.
  - The guideline notes the importance, when selecting among the SSRIs, of considering the safety and acceptability of particular side effects for a given patient. Paroxetine was noted to be the SSRI most associated with weight gain.

Panic Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012*)
  - In acute panic attacks, reassurance of the patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines may be needed (eg, melting tablets). SSRIs and venlafaxine are the first-line treatments for panic disorder. After remission, treatment should continue for at least several months in order to prevent relapses. SSRIs, venlafaxine, TCAs, benzodiazepines and other drugs have shown long-term efficacy in these studies.

- **APA Practice Guideline for the Treatment of Panic Disorder** *(APA 2009)*
  - The use of a SSRI, SNRI, TCA, or CBT as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous RCTs. In the absence of a co-occurring mood disorder, monotherapy with a benzodiazepine is also an appropriate initial treatment.
    - The relatively favorable safety and side-effect profile of SSRIs and SNRIs makes them the best initial pharmacotherapy choice for many patients with panic disorder.
  - A particular form of psychodynamic psychotherapy, panic-focused psychodynamic psychotherapy (PFPP), was effective in 1 RCT and could be offered as an initial treatment.
  - There is insufficient evidence to recommend any of these pharmacological or psychosocial interventions as superior to another, or to routinely recommend a combination of treatments over monotherapy, although a combination may be chosen based on individual circumstances.

PMDD

- **American Family Physician – PMS and PMDD** (*Hofmeister and Bodden 2016*)
  - SSRIs are first-line treatment for severe symptoms of PMS and PMDD. Sertraline, paroxetine, fluoxetine, citalopram, and escitalopram can be used to treat the psychiatric symptoms of PMS and PMDD and have been shown to relieve some of the physical symptoms.

  - A 2013 Cochrane review analyzed 31 RCTs that compared SSRIs with placebo for symptom relief of PMS. Each of the 5 SSRIs studied had statistically significant benefits on patient-reported symptoms when taken continuously or only during the luteal phase, but more direct studies comparing luteal phase administration with continuous administration are needed.
- SNRIs such as venlafaxine have been used off-label to treat PMDD in women with predominantly psychological symptoms. The effect is achieved over a relatively short period, 3 to 4 weeks, and sustained throughout subsequent menstrual cycles.

PTSD

- **VA/DoD Clinical Practice Guideline for the Management of PTSD** *(VA/DoD 2017*)
  - For those patients who choose not to engage in or are unable to access trauma-focused psychotherapy, the use of sertraline, paroxetine, fluoxetine, or venlafaxine as monotherapy is recommended based on the results of 3 systematic reviews. Each of these 3 meta-analyses concluded that sertraline, paroxetine, fluoxetine, and venlafaxine each had stronger evidence to support use in the treatment of PTSD compared to the other SSRIs and SNRIs. The benefits of these medications also outweigh the potential harms.
- **APA Practice Guideline for the Treatment of Acute Stress Disorder and PTSD** *(APA 2004, APA 2009 [update])*
  - The 2004 guideline recommended the SSRIs as a first-line medication treatment for patients with PTSD. The trials reviewed in the 2009 update suggest that the SSRIs may no longer be recommended with the same level of confidence for veterans with combat-related PTSD as for patients with non-combat-related PTSD. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment.
  - No significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available.

Social Anxiety Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012*)
  - The guideline recommends SSRIs and venlafaxine for first-line pharmacologic therapy for social anxiety disorder. There is insufficient evidence to recommend benzodiazepines or TCAs. Exposure therapy and CBT are also effective psychotherapies.

Bulimia Nervosa

- **APA Practice Guideline for the Treatment of Eating Disorders** *(APA 2012)*
  - In a 2011 systematic review for the WFSBP, *Aigner et al* identified 36 RCTs of medications for the treatment of bulimia nervosa. They reported that for TCA, Grade A evidence exists with a moderate risk-benefit ratio. For fluoxetine, Grade A evidence exists with a good risk-benefit ratio, and for topiramate, there is Grade A evidence with a moderate risk-benefit ratio. These findings and recommendations were consistent with the 2006 APA guideline, which recommends antidepressants, particularly the SSRIs, as one effective component of the initial treatment program for most patients with bulimia nervosa.
  - Other pharmaceutical agents, including oxcarbazepine, aripiprazole, and baclofen, have been reported to be effective for bulimia nervosa, but the results were from small case series or studies sponsored by the drug manufacturer.
  - Citalopram was studied in a small single-blind 12-week RCT. In this study, 37 patients with bulimia nervosa received fluoxetine (20 to 60 mg/day) or citalopram (20 to 40 mg/day). Both groups improved with respect to eating pathology. Patients receiving fluoxetine reported greater reductions in introjected anger, whereas those receiving citalopram reported greater reduction in depressive feelings.

SAFETY SUMMARY

- SSRIs are contraindicated in patients receiving MAOIs or within 14 days of their discontinuation.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking SSRIs.
- The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely. Drugs that have serotonergic properties include meperidine, triptans, most antidepressants, amphetamines, ergot alkaloids, dopamine antagonists, St. John's wort, and others. Additionally, SSRIs should not be administered with an SNRI or another SSRI as the risk for serotonin syndrome or neuroleptic malignant syndrome is greatly increased.

- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate one SSRI may do well with another. Common AEs are summarized in the table below *(Hirsch and Birnbaum 2017)*.

Table 3. AEs of SSRIs

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity¶	Weight gain	Sexual dysfunction
Citalopram	0	0	1+	1+	1+Δ	1+	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+	4+
Sertraline	0	0	2+	1+	0 to 1+	2+◊	1+	3+

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects.

¶ All SSRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

Δ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations.

◊ Sertraline is associated with higher rates of diarrhea.

DOSING AND ADMINISTRATION

Table4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brisdelle (paroxetine mesylate)	Capsules	Oral	Once daily at bedtime	--
Celexa (citalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	• Dosing adjustment in hepatic impairment; use with caution in severe renal impairment
fluoxetine DR	Capsules	Oral	Once weekly	• Initiate fluoxetine DR capsules 7 days after the last daily dose of fluoxetine 20 mg • Dosing adjustment in hepatic impairment
Fluvoxamine	ER capsules, tablets	Oral	Capsules: once daily at bedtime Tablets: once daily at bedtime for total daily doses ≤ 50 mg (pediatric) or ≤ 100 mg (adults); divided in 2 doses for total daily doses > 50 mg (pediatric) or > 100 mg (adults)	• Dosing adjustment in hepatic impairment
Lexapro (escitalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	• Dosing adjustment in hepatic impairment; use

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with caution in severe renal impairment
Paxil (paroxetine hydrochloride)	Oral suspension, tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in renal or hepatic impairment
Paxil CR (paroxetine hydrochloride)	Tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in renal or hepatic impairment
Pexeva (paroxetine mesylate)	Tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in severe renal or hepatic impairment
Prozac (fluoxetine)	Capsules, oral solution, tablets	Oral	Once daily, in the morning or twice a day	• Dosing adjustment in hepatic impairment
Sarafem (fluoxetine)	Capsules, tablets	Oral	Once daily, given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle)	• Dosing adjustment in hepatic impairment
Zoloft (sertraline)	Oral solution, tablets	Oral	Once daily	• Dosing adjustment in mild hepatic impairment; not recommended in moderate to severe hepatic impairment

See the current prescribing information for full details

CONCLUSION

- SSRIs are frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose.
- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The effectiveness is generally comparable between classes and within classes of SGAs. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*APA 2010, Qaseem et al 2016, VA/DoD 2016*).
- Some of the SSRIs are also FDA-approved to treat other psychiatric disorders besides MDD, including panic disorder, OCD, GAD, social anxiety disorder, PTSD, PMDD, and bulimia nervosa. For these various indications, there are generally no significant differences among the SSRIs; however, some products do have a stronger level of evidence or more clinical data available.
- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate 1 SSRI may do well with another. AEs include: drowsiness, insomnia, QTc prolongation, orthostatic hypotension, weight gain, and sexual dysfunction.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors, with an increased risk in children, adolescents, and young adults taking SSRIs. The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely.

REFERENCES

- American Psychiatric Association Practice Guideline for the Treatment of Patients with Eating Disorders, Third Edition. August 2012. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/eatingdisorders-watch.pdf. Accessed October 6, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. November 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed October 6, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (Guideline Watch). March 2013. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd-watch.pdf. Accessed October 6, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition. January 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf. Accessed October 6, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder. November 2004. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf. Accessed October 6, 2017.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (Guideline Watch). March 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd-watch.pdf. Accessed October 6, 2017.
- Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol*. 2013;28(1):33-45.
- Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84.
- Bighelli I, Trespidi C, Castellazzi M, et al. Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database Syst Rev*. 2016;9:CD011567.
- Brisdelle [package insert], Roswell, GA: Sebela Pharmaceuticals Inc.; March 2017.
- Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults. UpToDate Web site. www.uptodate.com. Updated April 25, 2016. Accessed October 6, 2017.
- Canton J, Scott KM, Glue P. Optimal treatment of social phobia: systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2012;8:203-15.
- Celexa tablets [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-58.
- Citalopram oral solution [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp.; January 2017.
- Engel S, Steffen K, Mitchell JE. Bulimia nervosa in adults: Clinical features, course of illness, assessment, and diagnosis. UpToDate Web site. www.uptodate.com. Updated March 6, 2017. Accessed October 7, 2017.
- Fluoxetine delayed-release [package insert], Dr. Reddy's Laboratories Limited; September 2015.
- Fluoxetine tablets [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2016.
- Fluvoxamine [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; February 2017.
- Fluvoxamine extended-release [package insert], Parsippany, NJ: Actavis Pharma, Inc.; March 2015.
- Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med*. 2011;155(11):772-85.
- Hirsch M, Birnbaum RJ. Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects. UpToDate Web site. www.uptodate.com. Updated August 15, 2017. Accessed October 6, 2017.
- Hofmeister S, Bodden S. Premenstrual Syndrome and Premenstrual Dysphoric Disorder. *Am Fam Physician*. 2016;94(3):236-40.
- Hoskins M, Pearce J, Bethell A, et al. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. *Br J Psychiatry*. 2015;206(2):93-100.
- Lexapro [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Marjoribanks J, Brown J, O'Brien PM, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2013;(6):CD001396.
- Paxil [package insert], Weston, FL: Apotex Corp.; October 2016.
- Paxil CR [package insert], Weston, FL: Apotex Corp.; October 2016.
- Pexeva [package insert], Roswell, GA: Sebela Pharmaceuticals Inc.; January 2017.
- Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. Nations Center for Health Statistics (NCHS) data brief, no 172. 2014. https://www.cdc.gov/nchs/data/databriefs/db172.htm. Accessed October 6, 2017.
- Prozac [package insert], Indianapolis, IN: Lilly USA, LLC; March 2017.
- Qaseem A, Barry MJ, Kansagara D, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;164(5):350-9.
- Sarafem [package insert], Irvine, CA: Allergan USA, Inc.; January 2017.
- Simon G. Unipolar major depression in adults: Choosing initial treatment. UpToDate Web site. www.uptodate.com. Updated December 23, 2015. Accessed October 6, 2017.
- Simpson HB. Obsessive-compulsive disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis. UpToDate Web site. www.uptodate.com. Updated March 6, 2016. Accessed October 6, 2017.
- Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008;(1):CD001765.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines for the management of major depressive disorder. Department of Veterans Affairs Web site. April 2016. https://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed October 6, 2017.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines for the management of posttraumatic stress disorder and acute stress reaction. Department of Veterans Affairs Web site. June 2017. https://www.healthquality.va.gov/guidelines/mh/ptsd/. Accessed October 6, 2017.
- Yonkers KA, Casper RF. Clinical manifestations and diagnosis of premenstrual syndrome and premenstrual dysphoric disorder. UpToDate Web site. www.uptodate.com. Updated February 10, 2016. Accessed October 6, 2017.

• Zoloft [package insert], New York, NY: Pfizer Inc.; June 2017.

Publication Date: October 16, 2017

INTRODUCTION

- Generalized anxiety disorder (GAD) is a common form of anxiety disorder characterized by excessive and uncontrollable worry that may manifest itself in a number of psychic and somatic symptoms such as irritability, difficulty concentrating, muscle tension, fatigue, and sleep disturbance. To meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria, worry and other associated symptoms must be present more days than not for at least 6 months and must adversely affect the patient's life (*Baldwin et al 2018, DSM-V criteria*).
  - According to the National Institutes of Mental Health (NIMH), the 12-month prevalence of GAD is 2.7% in the United States (US) population *(NIMH Web site 2017).*
  - The onset of GAD symptoms may occur before the age of 20. GAD is twice as common in females compared to males, and is the most common anxiety disorder among older patients *(Baldwin et al 2018).*
- Social anxiety disorder (SAD) is characterized by the persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with SAD often avoid social interactions or endure them with intense anxiety or distress *(Bandelow et al 2012).*
- Panic disorder is a form of anxiety disorder that is characterized by episodic, unexpected panic attacks that occur without a clear trigger. Panic attacks are defined by the rapid onset of intense fear (typically peaking within about 10 minutes) with at least 4 of the physical and psychological symptoms listed in the DSM-V diagnostic criteria (ie, palpitations, sweating, trembling/shaking, sensations of shortness of breath, feelings of choking, chest pain/discomfort, nausea, feeling dizzy or unsteady, chills or heat sensations, paresthesias, derealization, fear of losing control, and fear of dying) *(Locke et al 2015).*
- Effective treatments for GAD include cognitive-behavioral therapy, applied relaxation, and medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) *(Baldwin et al 2018).* Other agents, such as buspirone and hydroxyzine are also recommended as treatment options in clinical guidelines. The medication choice should be made based on several factors, such as efficacy, possible adverse events (AEs), contraindications, and drug interactions *(Bandelow et al 2015).*
  - Benzodiazepines (BZDs) have been widely used in managing GAD because of their rapid onset of action and proven efficacy. They can be helpful as short-term treatment during the period before antidepressants take effect and to help alleviate the restlessness and agitation that can occur with initiation of antidepressant therapy. All of the BZDs are considered to be of equal efficacy for the treatment of GAD *(Gliatto 2000, Locke et al 2015).*
    - BZDs exert their effects through their activity at the gamma-aminobutyric acid type A (GABA) receptors, potentiating the effects of endogenous GABA, the main inhibitory neurotransmitter.
- Insomnia is defined as a complaint of trouble initiating or maintaining sleep, which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep *(Sateia et al 2017)*.
  - Insomnia is considered chronic when it has persisted for at least 3 months at a frequency of at least 3 times per week. The prevalence of chronic insomnia in industrialized nations is estimated to be at least 5% to 10%.
  - Insomnia is considered short-term when the disorder meets symptom criteria but has persisted for less than 3 months. Occasional, short-term insomnia is thought to affect 30% to 50% of the population.
- Insomnia often occurs with comorbid disorders, including depression, anxiety, and substance abuse *(Schutte-Rodin et al 2008)*.
  - Certain medical or psychiatric disorders may also increase the risk of insomnia; psychiatric and chronic pain disorders have been associated with insomnia in as many as 50 to 75% of patients.
  - Insomnia is also associated with an increased risk of suicide and may result in relapse among prior substance abusers.
- The primary treatment goals are to improve sleep quality and quantity and to improve insomnia-related daytime impairments *(Schutte-Rodin et al 2008)***.**

- General treatment measures for insomnia include the treatment of comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimizing the sleep environment. Part of the initial approach to treatment should include cognitive behavioral therapy (*Sateia et al 2017, Schutte-Rodin et al 2008)*.
- Prior to the introduction of BZDs, barbiturates and related compounds were commonly used for the management of anxiety and sleep disturbance. The first BZD, chlordiazepoxide, was introduced to the US market in 1963, followed shortly by diazepam. Flurazepam, the first BZD approved as a hypnotic, became available in 1970 and rapidly supplanted the use of barbiturates and other related compounds for the treatment of insomnia. Zolpidem, the first non-BZD hypnotic approved in the US, became available in 1992 and remains the most widely prescribed hypnotic medication *(Sateia et al 2017)*.
- Other than zolpidem, the non-BZD sedative hypnotics used to treat insomnia are doxepin (Silenor), eszopiclone (Lunesta), ramelteon (Rozerem), lemborexant (Dayvigo), suvorexant (Belsomra), tasimelteon (Hetlioz), and zaleplon (Sonata).
  - Ramelteon and tasimelteon are melatonin receptor agonists that possess affinity for the MT1 and MT2 receptors vs. the MT3 receptor. Tasimelteon has a unique indication for treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), a circadian rhythm sleep disorder found predominantly in the blind and characterized by excessive sleepiness during the day and an inability to sleep at night.
  - Doxepin's mechanism of action is not fully understood, but it is thought that antagonism of the H1 receptor is the most likely mechanism by which doxepin exerts it sleep maintenance effect.
  - The remaining agents act at the GABA-receptor.
- All of the agents in this review (with the exception of tasimelteon) have been shown to result in positive effects on sleep latency, total sleep time (TST) and/or wake time after sleep onset (WASO). The BZDs have been shown to be effective in improving sleep latency and TST. Other agents such as zaleplon and ramelteon are effective in reducing sleep latency, whereas medications such as eszopiclone and temazepam are more likely to improve sleep maintenance *(Schutte-Rodin et al 2008)*.
- Although a substantial number of Food and Drug Administration (FDA)- and non FDA-approved anxiolytics and sedative hypnotics are available, the focus of this review will be on BZDs and non-BZDs agents. Other classes of agents such as barbiturates, SNRIs, SSRIs, and tricyclic antidepressants (TCAs) are also utilized in these settings but will not be the focus of this review.
- Several BZDs and some non-BZDs have additional FDA-approved indications such as alcohol withdrawal, seizure disorder, muscle relaxation, and depression. These indications are outside the scope of this review, and therefore will not be addressed in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Benzodiazepines	
Xanax (alprazolam), alprazolam Intensol, alprazolam ODT, Xanax XR (alprazolam extended-release)	✔
chlordiazepoxide	✔ §
Klonopin (clonazepam)	✔
Tranxene-T (clorazepate)	✔
Valium (diazepam), diazepam Intensol	✔
estazolam	✔ §
flurazepam	✔ §
Ativan (lorazepam), lorazepam Intensol	✔
oxazepam	✔ §
Restoril (temazepam)	✔
Halcion (triazolam)	✔
Doral (quazepam)	✔
Non-benzodiazepines	
buspirone	✔ §

Drug	Generic Availability
Silenor (doxepin)	✔
Lunesta (eszopiclone)	✔
Dayvigo (lemborexant)	-
meprobamate	✔
Rozerem (ramelteon)	✔
Belsomra (suvorexant)	-
Hetlioz (tasimelteon)	-
Sonata (zaleplon)	✔
Ambien, Edluar, Intermezzo, Zolpimist (zolpidem) Ambien CR (zolpidem extended-release)	✔ *

* Zolpimist is not available as generic
§ Buspar (buspirone), Dalmane (flurazepam), Librium (chlordiazepoxide), Prosom (estazolam), and Serax (oxazepam) are brands that are no longer marketed

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	BZDs												Non-BZDs									
Indication	**alprazolam**	**chlordiazepoxide**	**clonazepam**	**clorazepate**	**diazepam**	**estazolam**	**flurazepam**	**lorazepam**	**oxazepam**	**temazepam**	**triazolam**	**quazepam**	**buspirone**	**doxepin**	**eszopiclone**	**lemborexant**	**meprobamate**	**ramelteon**	**suvorexant**	**tasimelteon**	**zaleplon**	**zolpidem**
Short term treatment of insomnia characterized by difficulties with sleep initiation/onset																		✔				✔ (Ambien, Edluar, Zolpimist)
Treatment of insomnia, characterized by difficulties with sleep maintenance														✔								
Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance																✔			✔			✔ (Ambien CR)

Treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings						✔ *	✔					✔									
Short-term treatment of insomnia										✔	✔									✔	
Treatment of insomnia															✔						
Treatment of non-24-hour sleep-wake disorder																			✔		
As needed treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep																					✔ (Intermezzo)
Management of anxiety disorder or short-term relief of symptoms of anxiety	✔ (alprazolam Intensol, Xanax)	✔		✔	✔			✔	✔				✔				✔				
Treatment of generalized anxiety disorder	✔ (alprazolam ODT)																				
Treatment of panic disorder, with or without agoraphobia	✔ (alprazolam Intensol, alprazolam ODT, Xanax, Xanax XR)		✔																		
Preoperative apprehension and anxiety		✔																			
Pre-anesthesia to produce sedation, relief of anxiety, and decreased ability to recall events related to surgery								✔													

* Short-term use

(*Prescribing information: alprazolam Intensol 2017, alprazolam ODT 2019, Ambien 2019, Ambien CR 2019, Ativan 2018, Belsomra 2020, buspirone 2017, chlordiazepoxide 2016, Dayvigo 2019, diazepam Intensol 2016, Doral 2019, Edluar 2019, estazolam 2019, flurazepam 2018, Halcion 2019, Hetlioz 2019, Intermezzo 2019, Klonopin 2017, lorazepam*

Intensol 2019, Lunesta 2019, meprobamate 2016, oxazepam 2016, Restoril 2018, Rozerem 2018, Silenor 2019, Sonata 2019, Tranxene-T 2018, Valium 2017, Xanax 2017, Xanax XR 2016, Zolpimist 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A meta-analysis that examined 105 randomized, double-blind (DB), placebo-controlled (PC) trials was conducted to evaluate safety and efficacy of drug treatments for chronic insomnia in adults. Of these trials, 52 involved BZDs, 48 involved non-BZDs, and 8 involved antidepressants (ADPs). Most of the studies had short-treatment duration (≤ 4 weeks) in the non-elderly population. The primary efficacy measure was sleep onset latency, with WASO as the secondary outcome measure (*Buscemi et al 2007)*.
  - Sleep onset latency was significantly decreased, as compared to placebo, when measured by polysomnography (PSG) for the BZDs (weighted mean difference [WMD]: −10.0 minutes; 95% confidence interval [CI], −16.6 to −3.4), non-BZDs (WMD −12.8 minutes; 95% CI, −16.9 to −8.8) and ADPs (WMD −7.0 minutes; 95% CI, −10.7 to −3.3) as well as when measured by sleep diary (WMD −19.6 minutes; 95% CI, −23.9 to −15.3; WMD −17.0 minutes; 95% CI,−20.0 to −14.0; WMD: −12.2 minutes; 95% CI, −22.3 to −2.2, respectively).
  - WASO, sleep efficiency, TST, and sleep quality were evaluated and subcategorized by PSG and sleep diary. All results were statistically significant and favored BZDs and non-BZDs except for the PSG studies measuring WASO and TST, which were just below the range of significance. The PSG results significantly favored the antidepressants, and the sleep diary results, which were fewer, favored the antidepressants for WASO. Placebo was favored for TST, however, the results did not achieve statistical significance.
  - All treatment groups had a statistically significant incidence of AEs compared to placebo (BZDs risk difference [RD]: 0.15; non-BZDs RD: 0.07; and antidepressants RD: 0.09), although the most commonly reported AEs were considered minor. The most common AEs reported in the BZD group were headache, somnolence, dizziness, nausea, and fatigue while the most common AEs in the non-BZD and ADP groups were headache, dizziness, nausea, and somnolence. Indirect comparisons suggest that BZDs and non-BZDs have similar effects, but that non-BZDs may be safer.
  - The authors noted substantial heterogeneity of data, which was reduced in subgroup analyses by type of drug. Overall, BZDs and non-BZDs were not significantly different with respect to efficacy.
- A meta-analysis of 22 randomized, DB, PC trials evaluated the safety and efficacy of short-term (14 days) BZDs or zolpidem in the treatment of insomnia in adults < 65 years of age (n = 1894). The treatment duration was ≤ 35 days. It was found that BZDs and zolpidem produced significant improvements in the primary outcomes (as measured by PSG and self-reporting) of sleep onset latency, number of awakenings, TST, and sleep quality compared to placebo ($p < 0.001$) and their effect sizes were moderate *(Nowell et al 1997).*
- A 2012 meta-analysis that was published using data on the FDA website examined the efficacy and safety of non-BZDs (eszopiclone, zaleplon, zolpidem) using 13 randomized, DB, parallel-group (PG), PC clinical trials (n = 4378). Non-BZDs showed a small, but significant, improvement (reduction) of 22 minutes (95% CI, −33 to −11) in the primary endpoint of PSG sleep latency. For the other primary outcome of subjective sleep latency, non-BZDs showed a small but statistically significant improvement of 7 minutes, compared to placebo. The analyses of effects size showed significant but small to medium differences in PSG sleep latency (WMD -0.36; 95% CI, −0.57 to −0.16) and subjective sleep latency (WMD -0.33; 95% CI, −0.62 to −0.04). The secondary outcomes of TST, PSG and subjective number of awakenings, subjective sleep onset, and sleep quality did not show significant differences, which may have been due to limited data and reporting in the clinical trials *(Huedo-Medina et al 2012).*
- A 2017 meta-analysis of 31 randomized, PG, PC trials with BZDs, non-BZDs (eszopiclone, zaleplon, zolpidem), melatonin agonists, ADPs and other sedating medications was conducted to compare the efficacy of these medications for treatment of primary insomnia. In this meta-analysis, both BZDs and non-BZDs were significantly more effective than ADPs (including low-dose doxepin) in reducing objective sleep onset latency. Also, BZDs were found to be significantly more effective than non-BZDs in reducing subjective sleep onset latency. Non-BZDs demonstrated higher effect sizes for the primary outcomes of objective sleep onset latency and objective TST. Additionally, the pooled effect sizes for all of the outcome variables were statistically significant, indicating small to medium effects *(Winkler and Doering 2014).*
- A meta-analysis that evaluated 234 studies (n = 37,333) was conducted to determine the most efficacious pharmacological treatments for GAD, panic disorder, and SAD. The authors concluded that various studies with SSRIs

and SNRIs show that they can be efficacious in the management of anxiety. There was also some evidence for the efficacy of certain BZDs, buspirone, imipramine, hydroxyzine and trifluoperazine. BZDs, however, may cause dependency and are therefore not recommended for routine use *(Baldwin and Polkinghorn 2005).*

- A meta-analysis of 8 randomized controlled trials (n = 152) compared the effects of acetazolamide, temazepam, zolpidem, zaleplon, or theophylline on sleep quality in patients with acute exposure to high altitudes. The meta-analysis concluded that zaleplon and zolpidem improved the TST, sleep efficiency index, and stage 4 sleep duration, and these agents decreased WASO compared to placebo or no-treatment. Temazepam showed similar outcomes to placebo for the onset of sleep and sleep quality (*Kong et al 2018*).
- Two 6-month DB, PC, randomized trials (SET and RESET) of tasimelteon in totally blind patients with Non-24 (n = 84) demonstrated that tasimelteon 20 mg given 1 hour before bedtime at the same time every day was well tolerated and entrained the master body clock to a 24-hour clock as measured by urinary 6-sulfatoxymelatonin (aMT6s) and cortisol. During the SET clinical trial, the primary endpoint of sleep entrainment (as measured by aMT6s) was achieved by 20% (8 out of 40) of patients in the tasimelteon group vs. 3% (1 out of 38) of patients in the placebo group (difference of 17%, 95% CI: 3.2 to 31.6, p = 0.0171). A responder analysis demonstrated that 29% of subjects treated with tasimelteon demonstrated clinical response as measured by a ≥ 45-minute improvement in both nighttime and daytime sleep. During the RESET trial, 90% (9 out of 10) of patients in the tasimelteon group vs. 20% (2 out of 10) of patients in the placebo group maintained entrainment (*Lockley et al 2015*).
- A 12-month DB, PG, randomized clinical trial evaluated the safety and efficacy of suvorexant compared to placebo in patients with primary insomnia (n = 781). At Month 1, suvorexant showed greater efficacy than placebo in improving subjective sleep maintenance (TST 22.7 min, 95% CI: 16.4 to 29, p < 0.0001) and subjective time to sleep onset (TSO) (TSO -9.5 min, 95% CI: -14.6 to -4.5, p = 0.0002). These improvements were maintained throughout the 1-year phase (27.5 min in subjective TST, 95% CI: 16.2 to 38.8, p < 0.0001; -9.7 min in subjective TSO, 95% CI: -16.5 to -2.9, p = 0.0055). Over the course of 1 year, the proportion of patients with discontinuation due to AEs or serious AEs was similar among the treatment groups and there was no clinically important difference. The most common AE, somnolence, was reported for 13% of patients who received suvorexant and 3% who received placebo (difference of 10.5%, 95% CI: 6.8 to 14.1) *(Michelson et al 2014).*
- A meta-analysis of 4 randomized controlled trials (n = 3076) revealed improved TSO, subjective TST, and subjective quality of sleep at months 1 and 3 with suvorexant compared with placebo. At 12 months, suvorexant increased subjective TST, quality of sleep, but not TSO. Comparative trials of suvorexant to other agents are lacking (*Kuriyama et al 2017*).
- Two DB, PC, randomized studies evaluated the efficacy of lemborexant in patients with insomnia.
  - SUNRISE 1 randomized 1006 patients to lemborexant (5 mg or 10 mg), zolpidem CR, or placebo for 1 month. Compared with placebo, both doses of lemborexant displayed improved sleep onset from baseline (least squares means [LSM] treatment ratio 0.77; 95% CI, 0.67 to 0.89; p < 0.001 for lemborexant 5 mg, and LSM treatment ratio 0.72; 95% CI, 0.63 to 0.83; p < 0.001 for lemborexant 10 mg) and improved sleep efficiency (LSM treatment difference vs placebo 7.1%; 95% CI, 5.6% to 8.5%; p < 0.001 for lemborexant 5 mg, and LSM difference 8.0%; 95% CI, 6.6% to 9.5%; p < 0.001 for lemborexant 10 mg). Compared with zolpidem, both doses of lemborexant improved wake-after-sleep onset in the second half of the night (LSM treatment difference vs zolpidem -6.7 min; 95% CI, -11.2 to -2.2 min; p = 0.004 for lemborexant 5 mg, and LSM treatment difference -8.0 min; 95% CI, -12.5 to -3.5 min; p < 0.001 for lemborexant 10 mg) (*Rosenberg et al 2019*).
  - In the second study, 971 patients received lemborexant 5 mg, lemborexant 10 mg, or placebo. At 6 months, both doses of lemborexant demonstrated improvement in sleep onset, sleep efficiency, and WASO compared with placebo (p < 0.05 for all comparisons of lemborexant doses vs placebo) (*Dayvigo prescribing information 2019*).
- A meta-analysis with 48 studies was conducted to evaluate the efficacy of pharmacological treatments in GAD. The main drug classes compared were the BZDs (diazepam, lorazepam, alprazolam) and the azapirones (buspirone). The BZDs and azapirones were equally effective for anxiety (effect size for BZDs of 0.32, effect size for azapirones of 0.30), although the compliance rate was higher for the BZDs (24.4% drop-out rate vs. 30.7%, respectively, p < 0.05). The author concluded that BZDs and azapirones are effective for the short-term treatment of anxiety, but no drug class is superior in reducing symptoms *(Mitte et al 2005).*
- A Cochrane review of 24 randomized studies (n = 4233) concluded a possible superiority of BZDs for a response to treatment (risk ratio [RR] 1.65, 95% CI, 1.39 to 1.96) and dropout rate (RR 0.50; 95% CI, 0.39 to 0.64) compared with placebo among adult patients with panic disorder. The quality of the evidence was rated low for both outcomes (*Breilmann et al 2019*).

CLINICAL GUIDELINES

Anxiety

- American Academy of Family Physicians (AAFP) Diagnosis and Management of Generalized Anxiety Disorder and Panic Disorder in Adults *(Locke et al 2015)*
  - First-line pharmacologic therapies
    - SSRIs
    - SNRIs (duloxetine and venlafaxine ER)
    - buspirone
  - Second-line pharmacologic therapies
    - TCAs
    - pregabalin
    - quetiapine
    - hydroxyzine
  - Third-line pharmacologic therapies
    - Monoamine oxidase inhibitors (MAOIs)
  - The above therapies can be augmented with the addition of BZDs such as alprazolam, clonazepam, diazepam, and lorazepam.
- World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders *(Bandelow et al 2012)*
  - GAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, paroxetine, and sertraline)
        - SNRIs (venlafaxine, duloxetine)
        - pregabalin
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - Imipramine is recommended as second-line therapy
      - BZDs (alprazolam, diazepam) are recommended for patients without a history of dependency
      - Hydroxyzine may be an effective option, although it can cause sedation
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-refractory GAD patients, augmentation of SSRI treatment with atypical antipsychotics (risperidone or olanzapine) may be used.
  - SAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, fluvoxamine, paroxetine, and sertraline)
        - venlafaxine
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - The MAOI phenelzine is effective but less well tolerated than other antidepressants.
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-resistant cases, BZDs (clonazepam) may be used in patients without a history of dependency.
    - Recommendations, grade 4 (evidence from uncontrolled studies)
      - In treatment-resistant cases, the addition of buspirone to an SSRI was effective according to an open study.
- American Psychiatric Association practice guideline for the treatment of patients with panic disorder (second edition) *(Stein et al 2009)*
  - SSRIs, SNRIs, TCAs, and BZDs appear roughly comparable with regard to efficacy for panic disorder; however, SSRIs and SNRIs are recommended as first-line agents due to their relatively favorable safety profile.
  - BZDs may be used adjunctively with antidepressants to treat residual anxiety. BZDs may also be used as monotherapy or in combination with antidepressants for patients who are experiencing distressing symptoms that require rapid symptom control.
  - TCAs should be avoided in patients with acute narrow angle glaucoma or clinically significant prostatic hypertrophy. They may also increase the risk of falls in the elderly.

Insomnia

- American Academy of Sleep Medicine (AASM) Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults *(Sateia et al 2017)*
  - Recommendations for the treatment of sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended:
      - doxepin (low quality of evidence)
      - suvorexant (low quality of evidence)
    - The pharmacologic agents that are not recommended:
      - melatonin (very low quality of evidence)
      - tiagabine (low quality of evidence)
      - trazodone (moderate quality of evidence)
      - tryptophan (high quality of evidence)
      - valerian (low quality of evidence)
  - Recommendations for sleep onset and sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended:
      - eszopiclone (very low quality of evidence)
      - temazepam (moderate quality of evidence)
      - zolpidem (very low quality of evidence)
    - The pharmacologic agent that is not recommended:
      - diphenhydramine (low quality of evidence)
  - Recommendations for sleep onset insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended include:
      - ramelteon (very low quality of evidence)
      - triazolam (high quality of evidence)
      - zaleplon (low quality of evidence)
    - The pharmacologic agents that are not recommended:
      - melatonin (very low quality of evidence)
      - tiagabine (very low quality of evidence)
      - trazodone (moderate quality of evidence)
      - tryptophan (high quality of evidence)
      - valerian (low quality of evidence)
- American College of Physicians (ACP) Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guide *(Qaseem et al 2016)*
  - ACP recommends that all adults receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence).
  - ACP also recommends collaboration with the patient to determine whether a pharmacologic therapy should be initiated (Grade: weak recommendation, low-quality evidence).
    - Low-quality evidence shows that both eszopiclone and zolpidem improved global outcomes in the general population, and low- to moderate-quality evidence shows that eszopiclone, zolpidem, and doxepin improved sleep outcomes, such as sleep onset latency, TST, and WASO.
    - Moderate-quality evidence shows that suvorexant improved treatment response and sleep outcomes in mixed general and adult populations.
    - Low-quality evidence shows no statistically significant difference between ramelteon and placebo for sleep outcomes in the general population.
    - In older adults, low-quality evidence shows that eszopiclone improved global and sleep outcomes and both zolpidem and ramelteon decreased sleep onset latency.
    - Moderate-quality evidence shows that doxepin improved Insomnia Severity Index (ISI) scores, and low- to moderate-quality evidence shows that it improved sleep outcomes.
    - BZDs and melatonin were not included in these guidelines.
    - No one sedative hypnotic was recommended over another, due to insufficient evidence.

- Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (*VA/DoD 2019*)
  - The VA/DoD guideline recommends cognitive behavioral therapy (strong recommendation) and suggests brief behavioral therapy (weak recommendation) for chronic insomnia disorder. Cognitive behavioral therapy should be the first-line treatment over pharmacotherapy (weak recommendation).
  - Low-dose doxepin (ie, 3 mg or 6 mg) or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) are the recommended pharmacotherapies for short-course treatment of chronic insomnia disorder (weak recommendation).
  - The guideline recommends against using BZDs and trazodone for treating chronic insomnia disorder (weak recommendation).
  - The evidence remains insufficient to make recommendations regarding ramelteon or suvorexant for chronic insomnia disorder.

SAFETY SUMMARY

Contraindications

- MAOIs are contraindicated for concomitant use with buspirone and doxepin (or within 14 days of discontinuing an MAOI).
- Doxepin is contraindicated in patients with untreated narrow angle glaucoma or severe urinary retention.
- Suvorexant and lemborexant are contraindicated in patients with narcolepsy.
- Alprazolam products, estazolam, and triazolam are contraindicated with ketoconazole or itraconazole. Triazolam is also contraindicated with nefazodone and protease inhibitors.
- Alprazolam ODT, clonazepam, clorazepate, diazepam, and lorazepam are contraindicated in patients with acute narrow angle glaucoma.
- Clonazepam is contraindicated in patients with significant liver disease.
- Diazepam is contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea.
- Quazepam is contraindicated in patients with sleep apnea or chronic pulmonary insufficiency.
- Zolpidem products, eszopiclone, and zaleplon are contraindicated in patients with a prior history of complex sleep behaviors.

Warnings/Precautions

- Boxed warnings
  - BZDs carry a boxed warning for concomitant use with opioids, as it may result in profound sedation, respiratory depression, coma, and death.
  - Zolpidem products, eszopiclone, and zaleplon carry a boxed warning for complex sleep behaviors such as sleep-walking, sleep-driving, and other activities, which may lead to serious injuries, including death.
    - On April 30, 2019, the FDA mandated the addition of a boxed warning based on 66 cases of complex sleep behaviors with eszopiclone, zaleplon, or zolpidem leading to serious injuries, including death in 20 cases *(FDA Drug Safety Communication 2019)*.
- Daytime somnolence, sleep-walking, nighttime “sleep-driving,” and depression are listed as warnings for the majority of BZDs and non-BZDs in this review.
- Withdrawal effects can be observed after continuous long-term therapy with BZDs. Abrupt withdrawal or discontinuation should be avoided.
  - Withdrawal effects are mainly anxiety symptoms, but can also include autonomic instability (eg, diaphoresis, increased heart rate), insomnia, and sensory hypersensitivity. The most serious withdrawal effects are seizures and delirium tremens, which can occur with abrupt discontinuation.
- Severe anaphylaxis/anaphylactoid reactions (angioedema) have been reported with eszopiclone, flurazepam, quazepam, ramelteon, temazepam, zaleplon, and zolpidem.
- Worsening of symptoms of depression is considered a warning with most BZDs, doxepin, eszopiclone, zaleplon, zolpidem, lemborexant, and suvorexant.
- Pregnancy
  - All BZDs are considered highly teratogenic, especially during the first trimester.
  - Zolpidem use during the third trimester may lead to respiratory depression and sedation in neonates.

- Ramelteon shows a lack of a drug-associated risk for maternal and fetal outcomes based on postmarketing reports.
- Using meprobamate during the first trimester may lead to congenital malformations, and thus, meprobamate should be avoided during pregnancy.
- Other non-BZDs have not been studied in pregnant women and lack information on maternal or fetal outcomes in humans.

- Elderly
  - BZDs should be used cautiously in the elderly, ie, the lowest possible dose with slow dose up-titration should be utilized. Additionally, BZDs with a short half-life (eg, oxazepam) are preferred over those with a long half-life in the elderly patient population *(Gliatto 2000)*.
  - Zolpidem increases the risk of dizziness, drowsiness, and diarrhea in elderly patients.
  - Elderly patients have a 2-fold exposure to tasimelteon compared with younger patients.
  - With the non-BZDs, differences in the reported AEs between elderly and younger patients were not noted; however, older patients may be at a higher risk for drowsiness, and consequently, falls.

AEs

- Drowsiness, sedation, fatigue, cognitive impairment, and muscle weakness are the most frequent AEs with BZD use. Rare AEs include bradycardia, hypotension, rash, urticaria, blurred vision, diplopia, flushing, constipation, nausea, vomiting, change in libido, hepatic dysfunction, and abdominal pain.
- BZD use can lead to physiological dependence and tolerance, especially at higher doses and/or when given for a long duration. Treatment with BZDs should be limited to short-term use whenever possible. All BZDs are Schedule IV controlled substances.
- Somnolence/sedation and other central nervous system (CNS)-related AEs have also been reported with the non-BZD sedative hypnotics.

Drug Interactions

- In general, concomitant use of alcohol and other CNS depressants can increase the risk of CNS depression.
- The concomitant use of BZDs and opioids increases the risk of respiratory depression.
- Most BZDs (except lorazepam, oxazepam, and temazepam) are metabolized to some extent by cytochrome P450 (CYP) 3A4. Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) can increase the risk of toxicity while inducers of CYP3A4 (eg, rifampin) can decrease their effectiveness.
- With the non-BZDs (buspirone, ramelteon, lemborexant, suvorexant, zolpidem), there can be an increased toxicity risk when administered concomitantly with CYP3A4 inhibitors. The efficacy of buspirone, eszopiclone, lemborexant, suvorexant, ramelteon, tasimelteon, zaleplon, and zolpidem may be reduced when these agents are co-administered with CYP3A4 inducers (particularly with rifampin when administered with eszopiclone or ramelteon). Lemborexant may decrease the levels of CYP2B6 substrates (eg, methadone, bupropion).

Recalls

- On October 25, 2019, Mylan voluntarily recalled 1 lot of alprazolam tablets (lot number 8082708) due to the potential presence of foreign substances that may lead to infection *(Mylan Pharmaceuticals 2019)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
BZDs				
Alprazolam products				
alprazolam	tablets, oral concentrate, orally disintegrating tablets	Oral	3 times daily	A lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xanax XR	Extended-release tablets	Oral	Once daily	Administer in the morning; a lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease
Other BZDs				
chlordiazepoxide	Capsules	Oral	2 to 4 times daily	
clonazepam	Tablets	Oral	Twice daily	
clorazepate	Tablets	Oral	In divided doses or a single dose at bedtime	
diazepam	Tablets, oral concentrate, oral solution, injection	Oral, IV	2 to 4 times daily	
estazolam	Tablets	Oral	At bedtime	
flurazepam	Capsules	Oral	Before retiring	A lower dose is recommended for women, since they clear flurazepam from the body at a lower rate than men
lorazepam	Tablets, oral concentrate, injection	Oral, IV	2 to 3 times daily for anxiety or a single dose at bedtime for insomnia	
oxazepam	Capsules	Oral	3 to 4 times daily	
temazepam	Capsules	Oral	Before retiring	
triazolam	Tablets	Oral	Before bedtime	
quazepam	Tablets	Oral	At bedtime	
Non-BZDs				
buspirone	Tablets	Oral	Twice daily	Not recommended in patients with severe renal or hepatic impairment
doxepin	Tablets	Oral	Within 30 minutes of bedtime	A lower starting dose is recommended in the elderly
eszopiclone	Tablets	Oral	Immediately before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening	Do not exceed 2 mg in patients with severe hepatic impairment
lemborexant	Tablets	Oral	Immediately before bedtime, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment
meprobamate	Tablets	Oral	3 to 4 times daily	Not recommended in children < 6 years of age
ramelteon	Tablets	Oral	Within 30 minutes of bedtime	Not recommended in patients with severe hepatic impairment
suvorexant	Tablets	Oral	Within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
tasimelteon	Capsules	Oral	Before bedtime, at the same time every night	Not recommended in patients with severe hepatic impairment
zaleplon	Capsules	Oral	Immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep	Not recommended in patients with severe hepatic impairment
zolpidem products				
Edluar	Tablets	SL	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Intermezzo	Tablets	SL	Should be administered when patient wakes in the middle of the night, but has at least 4 hours of bedtime remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Zolpimist	Oral spray	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien	Tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien CR	Extended-release tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men

Abbreviations: IV = intravenous; SL = sublingual
See the current prescribing information for full details

CONCLUSION

- No specific sedative hypnotic in this review is considered preferable to the others, as each has been shown to have positive effects on sleep latency, TST, and/or WASO in placebo-controlled trials.
- Individual patients may respond differently to these medications and therapy selection, therefore, should be based on consideration of the patient's specific symptom pattern, patient preferences, comorbid disease states, concurrent medications, and the side effect profile for each option *(Schutte-Rodin et al 2008).*
- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent *(Schutte-Rodin et al 2008).*
- Tasimelteon is the only FDA-approved prescription product with proven efficacy for the treatment of Non-24 in totally blind patients.
- The recommended treatments for GAD include cognitive-behavioral therapy, applied relaxation, and preferred medications such as SSRIs and SNRIs *(Baldwin et al 2018).*
- Although numerous meta-analyses have been conducted with the anxiolytic and sedative hypnotic classes, they are limited by lack of availability of high quality evidence and considerable variability in design and methodology across clinical trials *(Sateia et al 2017)*.

- The 2019 VA/DoD guideline recommends low-dose doxepin or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) for short-course treatment of chronic insomnia disorder *(VA/DoD 2019)*.
- All of the BZDs and many of the non-BZD agents are Schedule IV controlled substances due to their propensity to cause physiological dependence. Withdrawal effects can be observed after continuous long-term therapy with many of these agents; therefore, abrupt withdrawal or discontinuation should be avoided.

REFERENCES

- Alprazolam ODT [package insert], Parsippany, NJ: Actavis Pharma, Inc; November 2019.
- Alprazolam Intensol [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp; March 2017.
- Ambien [package insert], Bridgewater, NJ: Sanofi-Aventis; August 2019.
- Ambien CR [package insert], Bridgewater, NJ: Sanofi-Aventis; August 2019.
- Ativan [package insert], Bridgewater, NJ: Valeant Pharmaceuticals LLC; October 2018.
- Baldwin D, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. *Int J Neuropsychopharmacol.* 2005;8(2):293-302.
- Baldwin D, Stein MB, Hermann R. Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis. UpToDate Web site. www.uptodate.com. Updated April 3, 2018. Accessed April 1, 2020.
- Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind, D. Efficacy of treatments for anxiety: a meta-analysis. *Int Clin Psychopharmacol.* 2015;30(4):183-192.
- Bandelow B, Sher L, Bunevicius R,et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84.
- Belsomra [package insert], Whitehouse Station, NJ: Merck & Co.; March 2020.
- Breilmann J, Girlanda F, Guaiana G, et al. Benzodiazepines versus placebo for panic disorder in adults. *Cochrane Database Syst Rev*. 2019;3:CD010677. doi: 10.1002/14651858.CD010677.pub2.
- Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007; 22(9):1335-50.
- Buspirone [package insert], Bridgewater, NJ: Amneal Pharmaceuticals LLC; April 2017.
- Chlordiazepoxide [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc; August 2016.
- Anxiety disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. http://dsm.psychiatryonline.org. PsychiatryOnline Web site. Accessed April 1, 2020.
- Dayvigo [package insert], Woodcliff Lake, NJ: Eisai, Inc. December 2019.
- Diazepam Intensol [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp; May 2016.
- Doral [package insert], Atlanta, GA: Galt Pharmaceuticals LLC; December 2019.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 1, 2020.
- Edluar [package insert], Somerset, NJ: Meda Pharmaceutics, Inc.; August 2019.
- Estazolam [package insert], Parsipanny, NJ: Actavis Pharma, Inc.; October 2019.
- FDA drug safety communication: FDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. US Food and Drug Administration Web site. Updated May 14, 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia. Accessed April 1, 2020.
- Flurazepam [package insert], Morgantown, WV: Mylan Pharmaceutics, Inc.; December 2018.
- Generalized anxiety disorder. NIH/NIMH Web site. Updated November 2017. https://www.nimh.nih.gov/health/statistics/prevalence/generalized-anxiety-disorder-among-adults.shtml. Accessed April 1, 2020.
- Gliatto MF. Generalized Anxiety Disorder. *Am Fam Physician*. 2000;62(7):1591-1600.
- Halcion [package insert], New York, NY: Pharmacia and Upjohn Company; October 2019.
- Hetlioz [package insert], Washington, DC: Vanda Pharmaceutics, Inc.; October 2019.
- Huedo-Medina TB, Kirsch I, Middlemass J et al. Effectiveness of non-benzodiazepine hypnotics in the treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ.* 2012;345:e8343.
- Intermezzo [package insert], Stamford, CT: Purdue Pharma; August 2019.
- Klonopin [package insert], South San Francisco, CA: Genentech USA Inc; October 2017.
- Kong F, Liu G, Xu J. Pharmacological agents for improving sleep quality at high altitude: a systematic review and meta-analysis of randomized controlled trials. *Sleep Med*. 2018;51:105-114. doi: 10.1016/j.sleep.2018.06.017.
- Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. *Sleep Med Rev*. 2017;35:1-7. doi: 10.1016/j.smrv.2016.09.004.
- Locke AB, Kirst N, Shultz C. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician* 2015;91(9):617-624.
- Lockley SW, Dressman MA, Licamele L, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386(10005):1754-64
- Lorazepam Intensol [package insert], Branchburg, NJ: Amneal Pharmaceuticals LLC; September 2019.
- Lunesta [package insert], Marlborough, MA: Sunovian Pharmaceutics, Inc.; August 2019.
- Meprobamate [package insert], Eatontown, NJ: Heritage Pharmaceuticals, Inc,; July 2016.
- Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2014;13:461-471.
- Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol.* 2005;25(2):141-150.

- Mylan Pharmaceuticals initiates voluntary nationwide recall of one lot of alprazolam tablets, USP C-IV 0.5 mg, due to the potential of foreign substance. Food and Drug Administration Web site. Updated October 26, 2019. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/mylan-pharmaceuticals-initiates-voluntary-nationwide-recall-one-lot-alprazolam-tablets-usp-c-iv-05. Accessed April 1, 2020.
- Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF 3rd, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA*. 1997; 278(24):2170-7.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 1, 2020.
- Oxazepam [package insert], Parsippany, NJ: Actavis Pharma, Inc.; September 2016.
- Restoril [package insert], St. Louis, MO: Mallinckrodt Pharmaceutics, Inc.; December 2018.
- Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. *JAMA Netw Open*. 2019 Dec 2;2(12):e1918254. doi: 10.1001/jamanetworkopen.2019.18254.
- Rozerem [package insert], Deerfield, IL: Takeda Pharmaceutics, Inc.; December 2018.
- Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guidelines for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(2):307-349.
- Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
- Silenor [package insert], Morristown, NJ: Currax Pharmaceuticals LLC; August 2019.
- Sonata [package insert], New York, NY: Pfizer, Inc.; August 2019.
- Stein MB, Goin MK, Pollack MH et al. American Psychiatric Association practice guideline for the treatment of patients with panic disorder. 2009. Psychiatry Online Web site. https://psychiatryonline.org/guidelines. Accessed on April 1, 2020.
- Qaseem A, Kangsara D, Forceia MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165:125-133.
- Tranxene-T [package insert], Lebanon, NJ: Recordati Rare Disease, Inc.; May 2018.
- Valium [package insert], Little Falls, NJ: Roche Laboratories Inc; June 2017.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines - the management of chronic insomnia disorder and obstructive sleep apnea. Department of Veterans Affairs Web site. October 2019. https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp. Accessed April 1, 2020.
- Winkler A, Doering B K. Drug treatment of primary insomnia: A meta-analysis of polysomnographic randomized controlled trials. *CNS Drugs*. 2014:28:799–816.
- Xanax [package insert], New York, NY: Pharmacia and Upjohn Company; January 2017.
- Xanax XR [package insert], New York, NY: Pharmacia and Upjohn Company; December 2016.
- Zolpimist [package insert], Englewood, CO: Aytu BioScience, Inc.; August 2019.

Publication Date: May 4, 2020

INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications generally exert their effect in part by blocking dopamine (D)-2 receptors (*Jibson et al 2017*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first-generation antipsychotics (FGAs), and atypical antipsychotics, also called second-generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Clinical Pharmacology 2020, Jibson et al 2017*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2 receptor in addition to D2.
  - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole and brexpiprazole act as partial agonists at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Cariprazine is a partial agonist at D2 and D3. Pimavanserin does not have dopamine blocking activity and is primarily an inverse agonist at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, schizoaffective disorder, and hallucinations and delusions associated with Parkinson's disease (PD) psychosis.
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman et al 2018*).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the U.S. reported a prevalence of 14.6 per 1000 children at age 8 in 2012 (*Morbidity and Mortality Weekly Report [MMWR] 2016*).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component, which alters brain development (*Augustyn 2017*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman et al 2018*).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be between 1 and 3%, although the true prevalence is uncertain (*Stovall 2018[a]*).
  - Genetics, in addition to environmental factors, appear to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2018[b]*).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Gelenberg et al 2010*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2013 to 2016, approximately 8.1% of individuals aged ≥ 20 years in the United States (U.S.) meet the criteria for depression. Women are more likely to experience symptoms of depression in their lifetime as compared to men (10.4% vs 5.5%) (*Centers for Disease Control and Prevention [CDC] Web site*).

- Schizophrenia
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Lehman et al 2004*).
  - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013*, *Lehman et al 2004*).
  - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
  - The prevalence of schizophrenia is approximately 0.25 to 0.64%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008*, *National Institute of Mental Health Web site, van Os et al 2009*).
  - The pathogenesis of schizophrenia is unknown, and may be related to disruption(s) in one or more neurotransmitter systems (*Fischer and Buchanan 2019*).
  - Symptoms of schizophrenia fall into 3 categories: positive symptoms (eg, hallucinations, delusions, disorganized thoughts and behavior), negative symptoms (eg, flat affect, decreased expressiveness, apathy), and cognitive symptoms (eg, impaired attention, memory, and executive functioning) (*Fischer and Buchanan 2020*).
- Tourette's disorder
  - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
  - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
  - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
  - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school-age children having had tics in the previous year.
- Parkinson's disease psychosis
  - Parkinson's disease is characterized by motor symptoms, which include tremor, bradykinesia, rigidity, and postural instability *(Bozymski et al 2017).*
  - Nonmotor symptoms can also occur in PD, which include autonomic dysfunction, sensory disturbances, and neuropsychiatric manifestations such as hallucinations, delusions, cognitive impairment, sleep disturbances, depression, and anxiety.
  - Approximately 60% of patients with PD develop psychosis.
  - For the diagnosis of PD psychosis, patients must meet the following criteria: primary diagnosis of PD; present with at least delusions, hallucinations, illusions, or false sense of presence; symptoms recurrent or continuous for at least 1 month; and exclusion of dementia-related psychosis or psychotic disorders.
- The agents included in this review are listed in Table 1 by brand name. Those drugs excluded from this review include Equetro (carbamazepine ER) capsule. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
  - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.
- Medispan class: Antipsychotics/Antimanic agents; Antipsychotics – Misc., Quinolinone derivatives, Dibenzo-oxepino Pyrroles, Dibenzodiazepines.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole tablets)	✔
aripiprazole orally disintegrating tablets (ODT), oral solution	✔ *
Abilify MyCite (aripiprazole tablet with sensor)	-†
Caplyta (lumateperone capsules)	-
Clozaril (clozapine tablets)	✔
Fanapt (iloperidone tablets)	-‡
clozapine ODT	✔ *
Geodon (ziprasidone hydrochloride [HCl] capsules)	✔
Geodon (ziprasidone mesylate injection)	✔
Invega (paliperidone extended-release [ER] tablets)	✔
Latuda (lurasidone tablets)	-‖
Nuplazid (pimavanserin tablets, capsules)	-
Rexulti (brexpiprazole tablets)	-
Risperdal (risperidone tablets, oral solution)	✔
risperidone ODT	✔ *
Saphris (asenapine sublingual tablet)	-§
Secuado (asenapine transdermal system)	-
Seroquel (quetiapine tablets)	✔
Seroquel XR (quetiapine ER tablets)	✔
Versacloz (clozapine oral suspension)	-
Vraylar (cariprazine capsules)	-
Zyprexa (olanzapine tablets, injection)	✔
Zyprexa Zydis (olanzapine ODT)	✔
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Aristada Initio (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Perseris (risperidone ER)	-
Risperdal Consta (risperidone microspheres)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine capsules)	✔

* Brand product discontinued; generic products are available.
† Abilify MyCite is the only drug-device combination product, comprised of a tablet with an embedded sensor, a wearable sensor patch, a smartphone application, and a web-based portal.
‡ Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products (*ME staff press release, 2016*). Alembic was granted tentative approval of a generic formulation in July 2018, but it is not yet marketed.
§ A generic formulation was approved in July 2018 but is not yet marketed.
‖ Generic formulations were approved in January 2019 but none are currently available.

(*Drugs@FDA 2020*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

- The following summarizes all FDA-approved indications:
  - Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
  - Bipolar disorder: All oral agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, brexpiprazole, pimavanserin, and ziprasidone mesylate. Aripiprazole ER (Abilify Maintena only) and Risperdal Consta are the only long-acting injectables indicated for the treatment of bipolar disorder.
    - Oral aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, asenapine, and lurasidone are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Oral olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
  - Depression: Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment-resistant depression.
  - Schizophrenia: All agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin, and the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in this class that is FDA-approved for treatment-resistant schizophrenia.
    - Oral aripiprazole (with the exception of tablets with sensor), lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
  - Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
  - Parkinson's disease psychosis: Pimavanserin is the first atypical antipsychotic FDA-approved for use in patients with PD psychosis.
  - Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.
- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Single Entity Products										
aripiprazole	✔ *	✔ *¶	-	-	✔ ¶	-	✔ *¶	-	✔ *	-
asenapine	-	✔ *¥	-	-	-	-	✔	-	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-	-
clozapine	-	-	-	-	-	✔	-	✔	-	-
iloperidone	-	-	-	-	-	-	✔	-	-	-
lumateperone	-	-	-	-	-	-	✔	-	-	-
lurasidone	-	-	✔ *	-	-	-	✔ *	-	-	-
olanzapine	-	✔ *	-	-	-	-	✔ *‖	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-	-
pimavanserin	-	-	-	-	-	-	-	-	-	✔
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-	-
ziprasidone HCl	-	✔	-	-	-	-	✔	-	-	-
ziprasidone mesylate	-	-	-	-	-	-	✔ §	-	-	-
Long-Acting Injectable Products										
aripiprazole ER (Abilify Maintena)	-	✔	-	-	-	-	✔	-	-	-
aripiprazole lauroxil ER (Aristada, Aristada Initio)	-	-	-	-	-	-	✔	-	-	-
paliperidone palmitate (Invega Sustenna)	-	-	-	-	-	✔	✔	-	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✔	-	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-	-

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
(Risperdal Consta)										
risperidone ER (Perseris)	-	-	-	-	-	-	✔	-	-	-
olanzapine pamoate ER (Zyprexa Relprevv)	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Products										
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-	-

Abbreviations: ER = extended release, IM = intramuscular, ODT = orally disintegrating tablet
*FDA-approved indications for pediatric patients.
† Indicated for the ER formulation.
‡ Patients must be observed by a health care professional for 3 hours post-dose administration with Zyprexa Relprevv.
§ IM injection indicated for acute agitation associated with schizophrenia.
‖IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.
¶ Indicated for the drug-device combination with tablet and sensor. The ability to improve patient compliance or modify aripiprazole dosage has not been established. The ability to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.
¥ Saphris sublingual tablets indicated for bipolar disorder, but not Secuado patches.

(*Prescribing information: Abilify 2020, Abilify Maintena 2020, Abilify MyCite 2020, Aristada 2020, Aristada Initio 2020, Clozaril 2020, Caplyta 2019, Fanapt 2017, Fazaclo 2020, Geodon 2020, Invega 2019, Invega Sustenna 2019, Invega Trinza 2019, Latuda 2019, Nuplazid 2019, Perseris 2019, Rexulti 2019, Risperdal 2020, Risperdal Consta 2020, Saphris 2017, Secuado 2019, Seroquel 2020, Seroquel XR 2020, Symbyax 2019, Versacloz 2020, Vraylar 2019, Zyprexa 2019, Zyprexa Relprevv 2019, Zyprexa Zydis 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SRs), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted an SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 with placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points with 5 mg/day, 2.5 with 10 mg/day, and 2.5 with 15 mg/day compared with 3.3 with placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (*Hirsch et al 2016*).
- A 2018 MA evaluated the efficacy of aripiprazole in patients with autism spectrum disorder (N = 408) and found aripiprazole significantly improved irritability, hyperactivity, and inappropriate speech but not social withdrawal compared with placebo. The RR for response rate was also improved with aripiprazole (RR, 2.08; 95% CI, 1.24 to 3.46) (*Maneeton et al 2018*).

- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (*Risperdal prescribing information 2020*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 kg vs 1 kg), pulse rate, and systolic blood pressure.
- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean change from baseline in ABC-I subscale score was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- A network MA evaluated 8 clinical trials (N = 878) with risperidone, aripiprazole, lurasidone, and placebo in pediatric autism spectrum disorder. Both risperidone and aripiprazole significantly reduced irritability compared with placebo with similar safety profiles. Lurasidone was not significantly different from placebo (*Fallah et al 2019*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania and depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo or asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in Young Mania Rating Scale (YMRS) score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and

showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).
- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).
- In a DB, PC trial, 347 patients aged 10 to 17 years were assigned to flexible doses of lurasidone 20 to 80 mg/day or placebo. The primary endpoint was change from baseline to week 6 in the CDRS-R total score. At week 6 of therapy, treatment with lurasidone was associated with a significant improvement compared with placebo in CDRS-R total score (-21.0 versus -15.3; $p<0.0001$). Lurasidone also was associated with statistically significant improvements in the Clinical Global Impression-Bipolar Severity depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning (*DelBello et al* 2017).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and

improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).

- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).
- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible-dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 with placebo (*Abilify prescribing information 2020*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2020*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most

clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, brexpiprazole, and pimavanserin. The following summarizes direct comparative evidence and recent MAs and SRs.
- A 2018 AHRQ SR of 156 trials concluded that symptoms of acute mania were modestly improved with asenapine, cariprazine, quetiapine, and olanzapine compared to placebo. Risperidone, ziprasidone, and paliperidone may also be effective for acute mania symptoms. Lithium was effective in the treatment of acute mania and prolonged the time to relapse compared to placebo, and this was the only agent that achieved a minimal clinically important difference in symptoms. All of these results were based on low-strength evidence because moderate and strong evidence was lacking (*Butler et al 2018*).
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).
- A SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapse; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short-term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 6 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011, Szegedi et al 2018*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[bJ*). A MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse

events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (*McIntyre et al 2009[b]*).

- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible-dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, drug steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to a pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- Meta-analyses have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Fornaro et al 2016, Ostacher 2017*, *Silva et al 2013, Taylor et al 2014, Vieta et al 2010*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

Major Depressive Disorder (MDD)

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as

adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.

- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics in combination with an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antipsychotic therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients (50 to 67 years), and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al 2005*). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 years (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).
  The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).

- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day doses (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo groups, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in this class review that is indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (p < 0.001) (*Thase et al 2007*). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic agents in this class review are indicated for use in schizophrenia with the exception of combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following is a summary of recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, cariprazine, iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).

- One large, recent Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short-term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approved agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There are limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year

(*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al 2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (*Kane et al 2011*). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (*Shoemaker et al 2010*). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).

- The approval of Secuado was based on the unpublished HP-3070-GL-04 clinical trial (N = 614), a 6-week, Phase 3, DB, PC, multinational, inpatient RCT. Patients with schizophrenia in an episode of acute exacerbation lasting ≤ 8 weeks and length of hospitalization ≤ 21 days were randomized to receive Secuado 3.8 mg (n = 204), Secuado 7.6 mg (n = 204), or placebo (n = 206) transdermal system once daily. Compared to placebo, both doses of Secuado demonstrated statistically significant improvements in PANSS total score ($p < 0.001$ for 3.8 mg; $p = 0.003$ for 7.6 mg) and CGI-S ($p < 0.001$ for both doses) (*FDA Secuado review 2020, Secuado prescribing information 2019*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible-dose study with no active comparator. In the flexible-dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR, it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A

flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95% CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; p < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (p = 0.85), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; p < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (p < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lumateperone was evaluated in a Phase 2 and two Phase 3 PC trials. All 3 trials enrolled patients who had demonstrated prior response to antipsychotic drug therapy (ie, not treatment-naïve and not treatment-resistant) who were experiencing an acute exacerbation of psychosis starting within the previous 4 weeks.
  - The Phase 2 trial (Study 005) was a 4-week RCT enrolling 335 patients (*Lieberman et al 2016*). Patients received lumateperone 42 mg daily (the marketed dose), lumateperone 84 mg daily, risperidone 4 mg daily, or placebo.
    - The primary endpoint was the change in total score on the PANSS. Results on the PANSS demonstrated LS mean changes of -7.4, -13.2, -8.3, and -13.4 in the placebo, lumateperone 42 mg, lumateperone 84 mg, and risperidone 4 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -5.8 (95% [CI, -10.5 to -1.1; multiplicity-adjusted p = 0.04), which was larger than that of the higher dose tested and comparable to that of risperidone.
  - The first Phase 3 trial (Study 301) was a 4-week RCT enrolling 450 patients (*Correll et al 2020*). Patients received lumateperone 42 mg daily, lumateperone 28 mg daily, or placebo.
    - Results for the PANSS total score (the primary endpoint) demonstrated LS mean changes of -10.3, -14.5, and -12.9 in the placebo, lumateperone 42 mg, and lumateperone 28 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -4.2 (95% CI, -7.8 to -0.6; multiplicity-adjusted p = 0.05).
    - The key secondary endpoint was the change in the CGI-S score. Results demonstrated LS mean changes of -0.5 for the placebo group and -0.8 for both lumateperone groups. The difference between lumateperone 42 mg and placebo was -0.3 (95% CI, -0.5 to -0.1; multiplicity-adjusted p = 0.05).

- The other Phase 3 trial (Study 302) enrolled 696 patients (*FDA Caplyta multidisciplinary review 2019*). It had a similar design to the previous studies, but had a duration of 6 weeks rather than 4 weeks. Patients received lumateperone 42 mg, lumateperone 14 mg, risperidone 4 mg, or placebo.
  - Results on the PANSS total score did not demonstrate a statistically significant efficacy benefit for either lumateperone dose vs placebo, with differences of 0.5 (95% CI, -2.9 to 3.8) and 0.1 (95% CI, -3.4 to 3.5) for the 42 mg and 14 mg doses, respectively. A significant difference for risperidone vs placebo was demonstrated (-5.4 [95% CI, -8.9 to -1.9]).
  - Results for secondary endpoints were not reported; the FDA reviewers deemed them irrelevant for discussion based on failure of the primary endpoint.

- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day) or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Parkinson's Disorder Psychosis

- Pimavanserin is the only oral atypical antipsychotic FDA-approved for the treatment of hallucinations and delusions associated with PD psychosis. The FDA-approval of pimavanserin was based on a 6-week PC, DB, RCT of 199 patients evaluating the safety and efficacy of pimavanserin 40 mg once daily. Compared to placebo, the least-squares mean difference of total PD adapted SAPS (SAPS-PD) score change from baseline at day 43 favored pimavanserin 40 mg (-3.06; 95% CI, -4.91 to -1.20; p = 0.0014). The most common adverse events in the pimavanserin vs the placebo group included urinary tract infection (13 vs 12%), falls (11 vs 9%), peripheral edema (7 vs 3%), hallucinations (7 vs 4%), nausea (6 vs 6%), confusion (6 vs 3%), and headache (1 vs 5%) *(Cummings et al 2014).*
- One MA of pimavanserin included 4 RCTs measuring the efficacy and safety compared to placebo in patients with PD psychosis. Pimavanserin was associated with a significant decrease in SAPS-hallucination and delusions score compared to placebo (weighted mean differences [WMD],-2.26; 95% CI, -3.86 to -0.67; p=0.005). Adverse effects were not significantly different from placebo, except pimavanserin was associated with a significantly lower incidence of orthostatic hypotension (RR, 0.33; 95% CI, 0.15 to 0.75; p = 0.008) *(Yasue et al 2016, Bozymski et al 2017)*.

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperdal Consta (risperidone microspheres) and Abilify Maintena (aripiprazole ER) are the only long-acting injections FDA-approved for bipolar I disorder in adults.
  - Abilify Maintena (aripiprazole ER) long-acting injection is indicated as maintenance monotherapy treatment (*Calabrese et al 2017*).
  - Risperdal Consta (risperidone microspheres) long-acting injection is indicated as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

- In a DB, PC, 52-week randomized withdrawal study (N = 266), aripiprazole ER injection significantly delayed recurrence of any mood episode compared with placebo, with a 55% reduction in risk of experiencing a mood episode over 1 year (HR, 0.45; 95% CI, 0.3 to 0.68). The proportion of patients experiencing recurrence of a manic episode was significantly less with aripiprazole ER injection (9.1 vs 30.1%); however, the recurrence rate for either depressive or mixed episodes was not different between treatment groups. After acute treatment of a manic episode with oral aripiprazole and transition to monotherapy with aripiprazole ER 400 mg intramuscularly (IM) once every 4 weeks (reduction to 300 mg was allowed for adverse reactions) for a 12-week stabilization period, patients were randomized to continue aripiprazole IM or withdrawal to placebo for 52 weeks. Of note, a large proportion of patients did not complete the study. Of the 266 randomized patients, 48.1% (N = 64) of the aripiprazole group and 28.6% (N = 38) of the placebo group completed the study. Treatment-emergent adverse effects that lead to discontinuation more commonly occurred with placebo (25.6 vs 17.4%); those that occurred more often with aripiprazole included weight gain of 7% or greater (18 vs 12.9%), akathisia (21.2 vs 12.8%), and anxiety (6.8 vs 4.5%) (*Calabrese et al 2017, Micromedex 2018*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Macfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 8 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada and Aristada Initio (aripiprazole lauroxil), Zyprexa Relprevv (olanzapine pamoate ER), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Risperdal Consta (risperidone microspheres), and Perseris (risperidone once-a-month injection). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (p = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (p < 0.001) and oral antipsychotics (p = 0.048) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; p = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (p = 0.02) and in preventing hospitalization (p = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (p = 0.65) (*Kishimoto et al 2014*).
- One MA compared outcomes for once-monthly long-acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not

be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).

- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (*Gentile et al 2013*).
- Recently-approved long-acting injectable agents include Aristada and Aristada Initio (aripiprazole lauroxil), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Perseris (risperidone once-a-month injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly IM injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*). In an indirect comparison of aripiprazole lauroxil (441 or 882 mg) and aripiprazole ER injection (400 mg), all treatment groups had similar reductions in symptoms of schizophrenia as measured by PANSS total score (*Cameron et al 2018*). The incidence of akathisia and changes in weight were also similar between treatments; although, the occurrence of treatment emergent adverse events was potentially lower with aripiprazole lauroxil 882 mg vs aripiprazole ER injection (OR, 0.46; 95% CI, 0.22 to 0.97).
    - Aristada Initio is indicated only to be used as a single dose in conjunction with oral aripiprazole for the initiation of Aristada, when used for the treatment of schizophrenia in adults. Effectiveness of Aristada Initio was established by adequate and well-controlled studies of oral aripiprazole and Aristada in adult patients with schizophrenia and a single pharmacokinetics bridging study (*Aristada Initio prescribing information 2020*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL, DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once-every-3-months injection. Paliperidone palmitate once-every-3-months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), increased weight (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (*Berwaerts et al 2015*).
  - The efficacy of risperidone ER monthly injection (Perseris) was evaluated in an 8-week, DB, randomized, PC trial in 354 patients who were experiencing an acute schizophrenia exacerbation. Patients received risperidone 90 mg, 120 mg, or placebo subcutaneously on days 1 and 29. LS squares mean change from baseline in PANSS total score (the primary outcome) was significantly greater with risperidone 90 mg (-6.148, $p = 0.004$) and 120 mg (-7.237, $p < 0.001$) compared to placebo. Compared to placebo, CGI-S scores were also significantly decreased in both risperidone dose groups ($p = 0.0002$ and $p < 0.0001$, respectively). Adverse effects were similar between groups, with the exception of weight gain (13% in the risperidone 90 mg group, 12.8% in the risperidone 120 mg group, and 3.4% in the placebo group) (*Nasser et al 2016*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010 [this guideline has been retired]*).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*; *Gelenberg et al 2010*).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, and suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009; Lehman et al 2004; VA Pharmacy Benefits Management Services 2012*).
- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder – According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or those taking drugs that have demonstrated QT prolongation. Lurasidone is

contraindicated for concomitant use with strong cytochrome (CYP) 3A4 inducers and/or inhibitors. Olanzapine/fluoxetine is contraindicated in patients taking concurrent pimozide or thioridazine due to the potential for QT prolongation, and in patients taking concurrent monoamine oxidase inhibitors due to the potential for serotonin syndrome. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.

- All atypical antipsychotic agents, including pimavanserin, have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome; this agent should not be used in patients with dementia-related psychosis. Lastly, clozapine-containing agents (ie, Clozaril, Fazaclo, and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors and cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Brexpiprazole: Pathological gambling and other compulsive behaviors.
  - Clozapine-containing products: Eosinophilia, hepatotoxicity, QT prolongation, pulmonary embolism, fever, and anticholinergic toxicity
  - Iloperidone: QT prolongation, hyperprolactinemia, and priapism
  - Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Lurasidone: Hyperprolactinemia and activation of mania/hypomania
  - Risperidone: Priapism, hyperprolactinemia, thrombotic thrombocytopenic purpura, increased sensitivity in patients with PD or dementia with Lewy bodies, and recent myocardial infarction or unstable cardiac disease
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, hyperprolactinemia, increased blood pressure in children and adolescents, leukopenia, neutropenia and agranulocytosis, and anticholinergic effects
  - Olanzapine: DRESS and hyperprolactinemia
  - Pimavanserin: QT prolongation
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling are required as part of both programs (*REMS@FDA 2019*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is February 28, 2019 (*FDA safety communication [clozapine] 2019*).
  - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Post-marketing reports of intense urges, particularly for gambling, have been reported in patients taking aripiprazole and brexpiprazole. Other compulsive urges include: sexual urges, shopping, eating or binge eating, and other compulsive behaviors have been reported. Dose reductions or stopping aripiprazole and brexpiprazole should be considered.
- In 2018, the FDA completed an analysis of reported postmarketing deaths and serious adverse events with the use of pimavanserin, including those reported to the FDA Adverse Event Reporting System (FAERS). The FDA did not identify any new or unexpected safety findings, or findings inconsistent with the established safety labeling. The FDA's conclusion was that the benefits of pimavanserin outweighed its risks for patients with hallucinations and delusions of Parkinson's disease psychosis (*FDA Drug Safety and Availability 2018*).
  - In assessing the reports of deaths, FDA considered that patients with Parkinson's disease have psychosis, a higher mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. In FAERS reports

that included a cause of death, there was no evident pattern to suggest a drug effect (*FDA Drug Safety and Availability 2018*).

- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with iloperidone, olanzapine, and ziprasidone.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Moderate	Low	Moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Negligible	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate
Hypercholesterolemia	Negligible	Negligible	Low	Negligible to low	Very high	Moderate	Negligible to low	Very high	Low	High	Low	Negligible to low

Abbreviation: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson et al 2017)*

DOSING AND ADMINISTRATION

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablet, tablet with sensor (drug/device), orally disintegrating tablet, oral solution	Oral	Daily Tablet with sensor has a patch which should be changed weekly or sooner, as needed.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. The MyCite (tablet with sensor) system is composed of an ingestible event marker (IEM) sensor, MyCite patch (wearable sensor), MyCite app, and a web-based portal for healthcare professionals and caregivers. Tablets with sensor may be administered with or without food. Most ingestions will be detected in 30 minutes to 2 hours. Patients should be instructed not to repeat doses if not detected.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Aristada Initio (aripiprazole lauroxil)			One dose of Aristada Initio 675 mg and aripiprazole 30 mg orally with the first Aristada injection	Must be administered by a healthcare professional. Avoid use in known CYP2D6 poor metabolizers, or with concomitant strong CYP2D6 inhibitors, and/or strong CYP3A4 inhibitors/inducers.
Saphris (asenapine)	Sublingual tablet	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Secuado (asenapine)	Patch	Transdermal	Daily	Patch should be applied once daily and left in place for 24 hours.
Rexulti (brexpiprazole)	Tablet	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers,

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsule, therapy pack	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablet	Oral	Once or twice daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Fazaclo (clozapine)	Orally disintegrating tablet			
Versacloz (clozapine)	Suspension			
Fanapt (iloperidone)	Tablet	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Caplyta (lumateperone)	Capsule	Oral	Once Daily	Should be administered with food. Moderate or strong CYP3A4 inhibitors: Avoid concomitant use.
Latuda (lurasidone)	Tablet	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Should be administered with food (≥ 350 calories).
Zyprexa (olanzapine)	Tablet	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablet			
Zyprexa IntraMuscular (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zyprexa Relprevv (olanzapine ER)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsule	Oral	Daily	The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. The safety of doses above 12 mg of olanzapine and 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Start olanzapine/fluoxetine at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine (female gender, geriatric age, nonsmoking status).
Invega (paliperidone ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.
Nuplazid (pimavanserin)	Tablet, capsule	Oral	One 34 mg capsule once daily; or one 10 mg tablet with	No initial dosage titration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			strong CYP3A4 inhibitors	Dosage adjustment is required with concomitant use with strong CYP3A4 inhibitors and/or inducers.
Seroquel (quetiapine)	Tablet	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablet, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablet			
Risperdal Consta (risperidone microspheres)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Perseris (risperidone ER)		SC	Monthly	
Geodon (ziprasidone)	Capsule	Oral	Twice daily	Give capsules with food. IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called FGAs, and atypical antipsychotics, also called SGAs (*Miyamato et al 2005*).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, MDD, schizophrenia, schizoaffective disorder, and PD psychosis. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in this class are indicated for use in schizophrenia with the exception of combination agent Symbyax (olanzapine/fluoxetine) and pimvanserin. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine is the only agent in this class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in this class are indicated for use in bipolar disorder,

except clozapine, iloperidone, paliperidone, pimavanserin, and brexpiprazole. Risperdal Consta and Abilify Maintena are the only long-acting injectables indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, lurasidone, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression. Pimavanserin is the only agent in the class FDA-approved for treatment of PD psychosis.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Lehman et al 2004, Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012, Clinical Pharmacology 2020*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2017; Micromedex 2020*). The following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in this class review; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
  - Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult

patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, and pimavanserin. However, fewer studies have been conducted with the newer agents.
  - Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
  - Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
  - Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In this class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
  - Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
  - Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.
- Cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2015*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2020*, *Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in PC trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of PD psychosis, pimavanserin has demonstrated safe and effective use compared to placebo. Pimavanserin was associated with a significantly lower incidence of orthostatic hypotension *(Cummings et al 2014, Yasue et al 2016, Bozymski et al 2017).*
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and

aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).

- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (*Findling et al 2014, Detke et al 2015*). Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only long-acting injection agents in this class that have demonstrated safe and effective use (*Calabrese et al 2017, Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011*).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

<u>Adults</u>

  - Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010*).
    - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
    - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
  - MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*, *Gelenberg et al 2010*).
    - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
  - Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012*).

- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

REFERENCES

- Abilify [package insert], Princeton, NJ: Otsuka America Pharmaceutical, Inc.; February 2020
- Abilify Maintena [package insert], Princeton, NJ: Otsuka America Pharmaceutical, Inc.;February 2020
- Abilify MyCite [package insert], Rockville, MD. Otsuka America Pharmaceutical, Inc.; February 2020
- Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation and second-generation antipsychotics in adults: Comparative Effectiveness Review. [Monograph on the internet]. Agency for Healthcare Research and Quality (AHRQ). Rockville, MD. 2012 Aug. No. 63. https://www.ncbi.nlm.nih.gov/books/NBK107254/pdf/Bookshelf_NBK107254.pdf. Accessed March 16, 2020
- Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. *J Child Adolesc Psychopharmacol*. 2008;18(3):227-236.
- American Psychiatric Association. Diagnostic and Statistical manual of Mental Disorders, 5th edition (DSM V). Washington, DC: In Section II, Depressive Disorders and Schizophrenia Spectrum and Other Psychotic Disorders. May 2013.
- Aristada [package insert], Waltham, MA: Alkermes, Inc.; February 2020.
- Aristada Initio [package insert], Waltham, MA: Alkermes, Inc.; February 2020.
- Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(11):CD006633.
- Asmal A, Flegar SJ, Wang J, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013:11:CD006625.
- Augustyn M. Autism spectrum disorder: terminology, epidemiology, and pathogenesis. UpToDate website. 2020. www.uptodate.com/. Accessed March 16, 2020.
- Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomized, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *Journal of Affective Disorders*. 2010;127:19-30.
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843-853.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia. *JAMA Psychiatry*. 2015;72(8):830-839.

- Biederman J, McDonnel MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectrums*. 2005;10(2):141-148.
- Bozymski KM, Lowe DK, Pasternak KM, et al. Pimavanserin: a novel antipsychotic for Parkinson's disease psychosis. *Ann Pharmacother.* 2017;51(6):479-487.
- Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar depression. *Int J Neuropsychopharmaco*l. 2009;12:773-782.
- Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, Thao V, Sunderlin B. Treatment for Bipolar Disorder in Adults: A Systematic Review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2018. doi 10.23970/AHRQEPCCER208
- Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; 76(3):284-292.
- Calabrese JR and Hertel P. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry*. 2017;78(3):324-331.
- Cameron C, Zummo Jacqueline, Desai D, et al. Efficacy and safety of aripiprazole lauroxil once monthly versus aripiprazole once-monthly long-acting injectable formulations in patients with acute symptoms of schizophrenia: an indirect comparison of two double-blind placebo-controlled studies. *Curr Med Res Opin*. Jan 2018:1-9. doi:10.1080/03007995.2017.1410471.
- Caplyta [package insert], New York, NY: Intra-Cellular Therapies, Inc.; December 2019.
- Capone GT, Goyal P, Grados M, et al. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: a naturalistic study. *J Dev Behav Pediatr*. 2008;29:106-116.
- Centers for Disease Control and Prevention (CDC). Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. CDC Web site. https://www.cdc.gov/nchs/products/databriefs/db303.htm. Accessed March 27, 2020.
- Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2012;27(2):76-90.
- Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. *Schizophrenia Research*. 2011;131:75-81.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol Clin Exp*. 2012;27:24-32.
- Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63(12):1762-1784.
- Clinical Pharmacology website. 2020. https://www.clinicalkey.com/pharmacology/. Accessed March 27, 2020.
- Clozaril [package insert], Rosemont, PA: HLS Therapeutics; March 2020.
- Correll CU, Davis RE, Weingart M, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial [published online ahead of print, 2020 Jan 8]. *JAMA Psychiatry*. 2020;10.1001/jamapsychiatry.2019.4379.
- Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(9):870-880.
- Corya SA, Williamson D, Sanger TM, et al . A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006;23:364-372.
- Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540.
- Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20-28.
- DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11:483-93.
- Detke HC, DelBello, MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-224.
- DelBello MP, Goldman R, Phillips D. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025. doi:10.1016/j.jaac.2017.10.006.
- Dixon L, Perkins D, Calmes C; for the American Psychiatric Association. Guideline Watch (September 2009): Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia-watch.pdf. Accessed March 30, 2020.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration website. 2020. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 30, 2020.
- Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015 [a]; 76(12):e1574-1582.
- Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2016;176(2-3):264-271.
- Durgam S, Greenberg WM, Li D, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234(2):199-209.
- Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.
- Durgam S, Starace A, Migliore R, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015[b];17(1):63-75.
- Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: A systematic review and network meta-analysis. *J Child Adolesc Psychopharmacol*. 2019. doi:10.1089/cap.2018.0115.

- Fanapt [package insert], Washington, D.C.: Vanda Pharmaceuticals Inc.; February 2017.
- Fazaclo [package insert], Palo Alto, CA: Jazz Pharmaceuticals; February 2020.
- FDA and Center for Drug Evaluation and Research (CDER). Summary Review: Vraylar (cariprazine). Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf. September 18, 2018. Accessed March 30, 2020.
- FDA Drug Safety and Availability: FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. Food and Drug Administration website. https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm?utm_campaign=FDA%20analysis%20finds%20no%20new%20or%20unexpected%20safety%20risks%20associated%20with%20Nuplazid&utm_medium=email&utm_source=Elogua. September 20, 2018. Accessed March 30, 2020
- FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Food and Drug Administration website. http://www.fda.gov/drugs/drugsafety/ucm461853.htm. January 15, 2016. Accessed March 30, 2020.
- FDA Drug Safety Communication: The Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program modification will go live on February 28, 2019. Food and Drug Administration website. http://www.fda.gov/drugs/drugsafety/ucm467560.htm. January 16, 2019. Accessed March 30, 2020.
- Food and Drug Administration (FDA). Caplyta (lumateperone) multidisciplinary review. December 20, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000MultidisciplineR.pdf. Accessed February 21, 2020.
- Food and Drug Administration (FDA). Secuado multi-discipline review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212268Orig1s000MultidisciplineR.pdf. January 24, 2020. Accessed February 25, 2020.
- Findling RL, Drury SS, Jensen PS, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. Approved by the AACAP Council on August 2, 2011. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf. Accessed March 30, 2020.
- Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041.
- Findling RL, Pathak S, Earley W, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325-335.
- Fischer BA, Buchanan RW. Schizophrenia in adults: clinical manifestations, course, assessment, and diagnosis. UpToDate Web site. Updated February 3, 2020. www.uptodate.com. Accessed February 10, 2020.
- Fischer BA, Buchanan RW. Schizophrenia in adults: epidemiology and pathogenesis. UpToDate Web site. Updated March 13, 2019. www.uptodate.com. Accessed February 10, 2020.
- Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsycholpharmacol*. 2016.pii:pyw076.
- Fornaro M, Stubbs B, De Barardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016;17(2):241.
- Fusar-Poli P, Kempton MJ, Rosenheck RA. Efficacy and safety of second-generation long-acting injections in schizophrenia: A meta-analysis of randomized-controlled trials. *Int Clin Psychopharmacol*. 2013;28(2):57–66.
- Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):39-47.
- Gelenberg AJ, Freeman MP, Markowitz JC, et al; for the American Psychiatric Association Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder. Third edition. Arlington, VA; 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed March 30, 2020.
- Gencer O, Emiroglu FNI, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: an open-label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;217-225.
- Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. *Pharmacotherapy*. 2013;33(10):1087-1106.
- Geodon [package insert], New York, NY: Pfizer Pharmaceuticals; January 2020.
- Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
- Glick ID, Correll CU, Altamura AC, et al. Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data driven, personalized clinical approach. *J Clin Psychiatry*. 2011;72(12):1616-1627.
- Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-Week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017 May 5. doi:10.1089/cap.2016.0189. [Epub ahead of print]
- Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurolo Sci*. 2011;32(6):1213-1217.
- Harvey PD, Ogasa M, Cucchiaro, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone. *Schizophrenia Research*. 2011;127:188-194.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016;(6):CD009043.
- Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder [monograph on the internet]. Arlington (VA): American Psychiatric Association; April 2002. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Accessed March 27, 2020.
- Hirschfeld RMA; for the American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder, 2nd ed. Arlington (VA): American Psychiatric Association; November 2005. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar-watch.pdf. Accessed March 27, 2020.
- Invega Sustenna [package insert], Titusville, NJ: Janssen Pharmaceuticals. Titusville, NJ January 2019.
- Invega Trinza [package insert], Titusville, NJ: Janssen Pharmaceuticals; January 2019.
- Jibson MD, Marder S, Herman R. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate website. 2020. www.uptodate.com. Accessed March 27, 2020.

- Jones MP, Nicholl D, Trakas K, et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. *Int J Clin Pharmacol Ther*. 2010;48(6):383-399.
- Kamijima K, Higuchi T, Ishigooka J, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). *J Affect Disord*. 2013;151(3):899-905.
- Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010[a];30:106-115.
- Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from three clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S29-S35.
- Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
- Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015[a];164(1-3):127-135.
- Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015[b]; 35(4):367-373.
- Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical anti*p*sychotics for schizophrenia. *Cochrane Database Syst Rev*. 2014;1:CD006569.
- Kishimoto T, Robenzadeh A, Leucht S, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192–213.
- Klemp M, Tvete IF, Skomedal T, et al. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of four atypical neuroleptic drugs compared to haloperidol and placebo. *J Clin Psychopharmacol*. 2011;31:698-704.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [a];(3):CD006654.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009[b]; (4):CD006627.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Quetiapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [b];(1):CD006625.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Risperidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2011;(1):CD006626.
- Komossa K, Rummel-Kluge, Schmid F, et al. Aripiprazole vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009[a];4:CD006569.
- Kumar A, Datta S, Wright S, et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev*. 2013 Oct 15;10:CD009582.
- Latuda [package insert], Marlborough, MA: Sunovion Pharmaceuticals, Inc.; December 2019.
- Lehman AF, Lieberman JA, Dixon LB, et al; for the American Psychiatric Association Work Group on Schizophrenia. Practice guideline for the treatment of patients with schizophrenia. Second edition. Arlington, VA; 2004. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed March 26, 2020.
- Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:2404-2412.
- Leucht S, Cipraini A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382: 951-962.
- Leucht S, Corves C, Arbter D, et al. Second-generation vs first-generation drugs for schizophrenia: a meta-analysis. *Lancet*. 2009[a];373:31-41.
- Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009[b];166:152-163.
- Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry*. 2016;79(12):952-961.
- Lieberman JA, Stroup TS, McElvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord*. 2017 ;213:138-150.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[a];171(2):169-177.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014[b];171(2):160-168.
- Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.
- Macfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009;11(8):827-839.
- Maneeton N, Maneeton B, Putthisri S, Suttajit S, Likhitsathian S, Srisurapanont M. Aripiprazole in acute treatment of children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2018;14:3063-3072. doi: 10.2147/NDT.S174622.
- Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156-165.
- Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
- Market Exclusive (ME) staff. Vanda Pharmaceuticals, Inc (NASDAQ:VNDA) Files An 8-K Other Events. [press release]. December 20, 2016. https://marketexclusive.com/vanda-pharmaceuticals-inc-nasdaqvnda-files-an-8-k-other-events-2/49544/. Accessed March 26, 2020.

- McClellan J, Kowatch R, Findling RL, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolec Psychiatry*. 2007;46(1):107-125.
- McClellan J, Stock S; for the American Academy of Children and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolec Psychiatry*. 2013;52(9):976–990.
- McCracken JT, McGough J, Shah J, et al. Risperidone in children with autism and serious behavioral problems (RUPP). *N Engl J Med*. 2002;347:314-321.
- McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry*. 2005;162:1142-1148.
- McGrath J, Saha S, Chant D, et al. Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76.
- McIntyre RS, Cohen M, Zhao J, et al. A three-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disorders*. 2009[a];11:673-686.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010[b];126:358-365.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010[a];122:27-38.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine vs olanzapine in acute mania: a double-blind extension study. *Bipolar Disorders*. 2009[b];11:815-826.
- Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.
- Meltzer L, Risinger R, Nasrallah M, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090.
- Micromedex Solutions website. 2020. http://www.micromedexsolutions.com/home/dispatch. Accessed March 25, 2020.
- Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone vs haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1-8.
- Miyamato S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry*. 2005;10:79-104.
- Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). *Neurology*. 2006;66(7):996-1002.
- Morbidity and Mortality Weekly Report (MMWR). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012. *MMWR Weekly*. 2016;65(3):1-23.
- Muralidharan K, Ali M, Silveira LE, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord*. 2013;150(2):408-414.
- Murphy TK, Lewin AB, Storch EA, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341-1359.
- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455.
- Nakamura M, Ogasa MS, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-836.
- Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol*. 2016;36(2):130-140. doi: 10.1097/JCP.0000000000000479
- National Institute of Mental Health (NIMH). Schizophrenia. NIMH website. https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml. Updated May 2018. Accessed March 25, 2020.
- Nuplazid [package insert], San Diego, CA: Acadia Pharmaceuticals, Inc.; March 2019.
- Nussbaum A and Stroup T. Paliperidone palmitate for schizophrenia. *Cochrane Database Syst Rev*. 2012;6:CD008296.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 25, 2020.
- Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. *World J Biol Psychiatry*. 2017:1-11.
- Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533-1540.
- Pagsberg AK, Tarp S, Glintborg D, et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):191-202.
- Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin-reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005;66(10):1326-1330.
- Perlis RH, Baker RW, Zarate CA, et al. Olanzapine vs risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006[a];67:1747-1753.
- Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006[b];76:509-516.
- Perseris [package insert]. North Chesterfield, VA: Indivior, Inc.; December 2019.
- Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: Systematic review update. Comparative Effectiveness Review No. 184. AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. https://www.ncbi.nlm.nih.gov/books/NBK442352/. doi: https://doi.org/10.23970/AHRQEPCCER184. Accessed March 25, 2020.
- Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68:1492-1500.

- Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase three studies. *J Clin Psychopharm*. 2008;28:S4-S11.
- Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2011;132:101-107.
- Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010;68(2):156-162.
- REMS@FDA. Food and Drug Administration website. 2020. http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed March 25, 2020.
- Rexulti [package insert], Rockville, MD: Otsuka Pharmaceuticals Co., Ltd; May 2019.
- Riedel M, Schennach-Wolff R, Dehning MS, et al. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum Psychopharmacol Clin Exp*. 2010; 25:116-125.
- Risperdal [package insert], Titusville, NJ: Janssen Pharmaceuticals; January 2020.
- Risperdal Consta [package insert], Titusville, NJ: Janssen Pharmaceuticals; January 2020.
- Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.
- Saphris [package insert], St. Louis, MO: Forest Pharmaceuticals; February 2017.
- Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010; 43:e1-e10.
- Secuado [package insert], Japan Saga Tosu: Hisamitsu Pharmaceutical Co., Inc.; October 2019.
- Seroquel [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2020.
- Seroquel XR [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2020.
- Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Phsychopharm*. 2011;26:130.
- Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634-e641.
- Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/ fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry*. 2005;66:1289-1297.
- Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013:146(3):310-318.
- Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med.* 2013;10(3):e1001403. doi: 10.1371/journal.pmed.1001403.
- Steffens DC, Nelson JC, Eudicone JM, et al: Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. *Int J Geriatr Psychiatry*. 2011; 26(6):564-572.
- Stovall J. Bipolar disorder in adults: epidemiology and pathogenesis. UpToDate website. 2020[a]. www.uptodate.com/. Accessed March 16, 2020.
- Stovall J. Bipolar mania and hypomania in adults: choosing pharmacotherapy. UpToDate website. 2020[b]. www.uptodate.com/. Accessed March 16, 2020.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Results of phase three of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1-12.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611-622.
- Symbyax [package insert], Indianapolis, IN: Eli Lilly and Company; November 2019.
- Szegedi A, Durgam S, Mackle M, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with acute manic or mixed episode associated with bipolar I disorder. *Am J Psychiatry*. 2018;175(1):71-79. doi: 10.1176/appi.ajp.2017.16040419.
- Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101.
- Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77.
- Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania-a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011;134:14-19.
- Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):452-469.
- Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
- Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015[b];76(9):1232-1240.
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015[a];76(9):1224-1231.
- Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.
- Van Os J, Kapur S. Schizophrenia. *Lance*t. 2009;374(9690):635-645.
- Versacloz [package insert], Tampa, FL: TruPharma, LLC.; February 2020.
- Veterans Administration (VA) and Department of Defense (DoD) Clinical Practice Guideline for Management of Major Depressive Disorder. VA/DoD website. April 2016. http://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed March 16, 2020.
- Veterans Administration (VA) Pharmacy Benefits Management Services. Antipsychotic selection algorithm schizophrenia. June 2012. http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations.asp. Accessed March 16, 2020.

- Veterans Administration (VA) Pharmacy Benefits Management Services; for the Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010 May. 176 p. http://www.healthquality.va.gov/bipolar/bd_305_full.pdf. Accessed March 16, 2020
- Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30:579-590.
- Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257.
- Vraylar [package insert], Irvine, CA: Allergan USA, Inc.; May 2019.
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. A pooled analysis of six-week acute-phase pivotal trials. *J Clin Psychopharmacol*. 2008;28:S12-S19.
- Weiden PJ, Manning R, Wolfgang CD, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. *CNS Drugs*. 2016;30(8):735-747.
- Weissman L, Bridgemohan C. Autism spectrum disorders in children and adolescents: overview of management. UpToDate website. 2020. www.uptodate.com/. Accessed March 16, 2020.
- Wen XJ, Wang LM, Liu ZL, et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Braz J Med Res*. 2014;47(7):605-616.
- Yasue I, Matsunaga S, Kishi T, et al. Serotonin 2A receptor inverse agonist as a treatment for Parkinson's disease psychosis: a systematic review and meta-analysis of serotonin 2A receptor negative modulators. *J Alzheimers Dis.* 2016;50(3):733-740.
- Yatham LN, Fallu A, Binder CE. A six-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007;(434):50-56.
- Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011;36:375-389.
- Yoo HK. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-e780.
- Yoon S, Jeon SW, Ko YH, et al. Adjunctive brexpiprazole as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2017;37(1):46-53.
- Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150-162.
- Zyprexa Relprevv [package insert], Indianapolis, IN: Eli Lilly and Company; October 2019.
- Zyprexa Zydis [package insert], Indianapolis, IN: Eli Lilly and Company; October 2019.
- Zyprexa [package insert], Indianapolis, IN: Eli Lilly and Company; October 2019.

Publication Date: 14th April 2020

Prior Authorization Guideline

Guideline Name	Fibromyalgia - Neuropathic Pain Agents

1 . Criteria

Product Name: Savella	
Guideline Type	Prior Authorization

Approval Criteria

1. Diagnosis of one of the following:

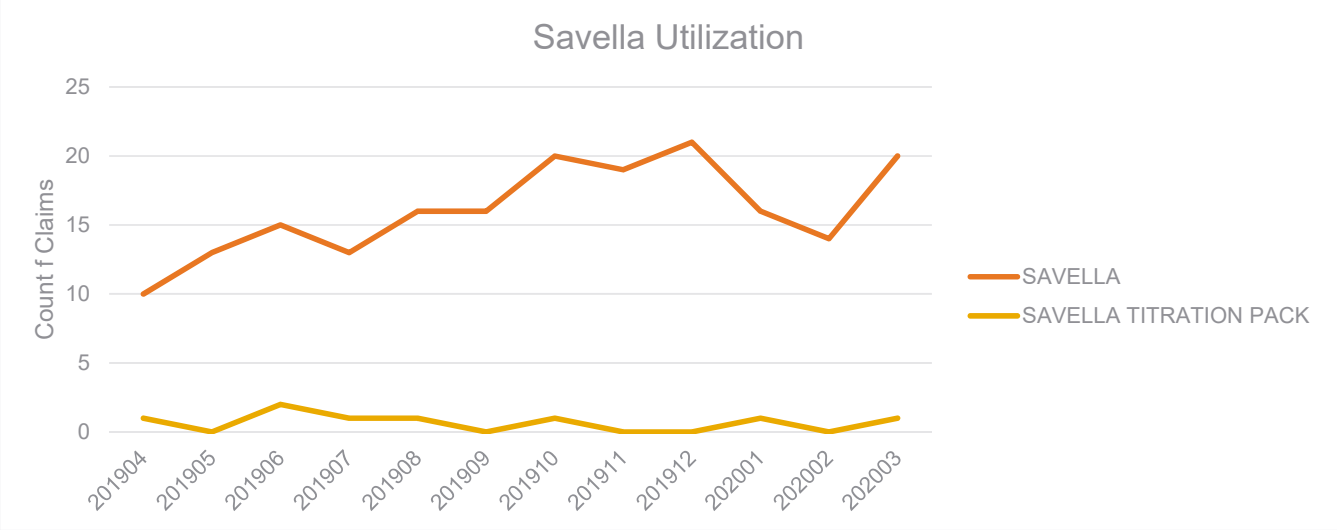
    1.1 Fibromyalgia

    1.2 Myalgia and myositis, unspecified

Nevada Medicaid

Savella Utilization
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Mem Count of Claims	Total Days Supply	Total Quantity
SAVELLA	32 193	7,183	15,244
SAVELLA TITRATION PACK	8 8	227	440



AA. Savella® (milnacipran)

Therapeutic Class: Fibromyalgia Agents: Serotonin-Norephinephrine Reuptake Inhibitor
Last Reviewed by DUR Board: June 3, 2010

Savella® (milnacipran) is subject to prior authorization.

Coverage and Limitations

1. Diagnosis of Fibromyalgia:

   a. If an ICD code for Myalgia and Myositis unspecified is documented on the prescription; or

   b. Completion of a prior authorization documenting a diagnosis of Fibromyalgia and/or Myalgia and Myositis, unspecified.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2017*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2019*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2018*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), and ZTlido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2019, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2019, Lyrica CR 2019, Neurontin 2019, Nucynta ER 2019, Qutenza 2013, Savella 2017, ZTLido 2018*).
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2018*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2019*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2019*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in established diabetic neuropathy is uncertain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2019*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2019*).
  - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (*Feldman et al 2019*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).

- Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2015*).

- The prevalence of fibromyalgia in the general U.S. population is estimated to be 2 to 3% and increases with age *(Goldenberg 2019)*. It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2015*).
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2015*).

PHN

- PHN refers to the persistence of the pain of herpes zoster beyond 4 months from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PNH are older age, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or life (*Bajwa et al 2019*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2019*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2019*). Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN *(Albrecht 2018).*
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2019*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✔
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	✔
Lyrica CR (pregabalin ER)	-
Neurontin (gabapentin)	✔
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✔					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔			
Adjunctive therapy for patients 1 month of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia	✔				✔					✔
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ §		
Management of neuropathic pain associated with spinal cord injury					✔					
Management of PHN		✔	✔		✔	✔	✔			
Relief of pain associated with PHN				✔					✔	
Moderate-to-severe primary restless legs syndrome			✔ ‡							
Treatment of generalized anxiety disorder	✔									
Treatment of major depressive disorder	✔									
Management of moderate to severe chronic pain in adults								✔ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
§ Indicated when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Medication is not for: use as an as-needed analgesic; pain that is mild or not expected to persist for an extended period of time; acute pain; or postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

(*Prescribing information: Cymbalta 2019, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2019, Lyrica CR 2019, Neurontin 2019, Nucynta ER 2019, Qutenza 2013, Savella 2017, ZTlido 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and Patient Global Impression of Change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by Brief Pain Inventory Modified Short Form (BPI-MSF) average pain (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Quilici et al 2009, Wernicke et al 2007[a], Wiffen et al 2017*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores compared to placebo, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score (*Lyrica prescribing information 2019*, *Siddall et al 2006, Vranken et al 2008*).

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with

the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).

- In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
- Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each drug (*Hauser et al 2010*).
- A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
- A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee et al 2016*).
- A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2018)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).
- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, short-form McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each

agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).

- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (n = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN support the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2019*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016 [update in progress 2020], recommend the following:
  - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
  - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
  - Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
  - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2020 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2020*).

- Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
- Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker.
- Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options.

- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear *(Attal et al 2010).*

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Duloxetine may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- Tapentadol ER should not be abruptly discontinued in patients who may be physically dependent on opioids. Rapid discontinuation in these patients may result in withdrawal symptoms, uncontrolled pain, and suicide. Mixed agonist/antagonist or partial agonist analgesics should not be used concomitantly with tapentadol ER.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.

- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. Methemoglobinemia has been reported in association with local anesthetic use.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin.
  - Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, MAOIs, linezolid, and methylene blue).
  - Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
  - Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
  - Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
  - Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.
  - Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Administer with evening meal Reduce dose in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	Administer with food Reduce dose in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Apply for up to 12 hours within a 24-hour period Caution in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min Administer after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Reduce dose in CrCl < 60 mL/min
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Do not use in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment Reduce dose in moderate hepatic impairment
Qutenza (capsaicin)	Patch	Transdermal	60-minute application of up to 4 patches every 3 months	Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	Reduce dose in CrCl < 30 mL/min Caution in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; ESRD = end-stage renal impairment
See the current prescribing information for full details

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrate that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2019, Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2019*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2018*).

REFERENCES

- Albrecht MA. Treatment of herpes zoster in the immunocompetent host. UpToDate Web site. Updated December 10, 2018. www.uptodate.com. Accessed January 29, 2020.
- American Diabetes Association (ADA). Microvascular complications and foot care: standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S135-S151. doi: 10.2337/dc20-s011.
- Armstrong DG, Chappell AS, Le TK, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes. *Pain Med.* 2007;8(5):410-418.
- Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-1344.

- Arnold LM, Hudson JI, Wang F, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with vs without major depressive disorder. *Clin J Pain*. 2009;25:461-468.
- Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain*. 2008;9(9):792-805.
- Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-e88.
- Backonja MM, Canafax DM, Cundy KC. Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. *Pain Medicine.* 2011;12:1098-1108.
- Backonja MM, Wallace MS, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol*. 2008;7(12):1106-1112.
- Bajwa ZH, Ortega E. Postherpetic neuralgia. UpToDate Web site. Updated July 31, 2019. http://www.uptodate.com/contents/postherpetic-neuralgia. Accessed January 29, 2020.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology.* 2011;76(20):1758-1765.
- Chou R, Carson S, Chan BK. Gabapentin vs tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. *J Gen Intern Med*. 2009;24(2):178-188.
- Clauw DJ, Mease P, Palmer RH, et al. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther*. 2008;30(11):1988-2004.
- Clauw DJ. Fibromyalgia: an overview. *Am J Med*. 2009;122(12 Suppl):S3-S13.
- Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52(4):1264-1273.
- Crofford LJ. Fibromyalgia. In: Jameson JL, Fauci A, Kasper DL, et al. eds. Harrison's Principles of Internal Medicine, 20e. New York, NY: McGraw-Hill; 2018. Accessed January 29, 2020.
- Cymbalta [package insert]. Eli Lilly and Company. Indianapolis, IN. October 2019.
- Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore, RA. Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2019;1:CD007076.
- Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;13(1):CD007393.pub4.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 29, 2020.
- Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60:1274-1283.
- Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132(3):237-251.
- Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. *Ann Pharmacother*. 2011;45:1483-1490.
- FDA Approved Risk Evaluation and Mitigation Strategies (REMS). Opioid analgesic REMS program. Food and Drug Administration Web site. Updated September 2018. https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems. Accessed January 29, 2020.
- Feldman EL, McCulloch DK. Management of diabetic neuropathy. UpToDate Web site. Updated November 22, 2019. https://www.uptodate.com/contents/management-of-diabetic-neuropathy. Accessed January 29, 2020.
- Feldman EL. Epidemiology and classification of diabetic neuropathy. UpToDate Web site. Updated March 14, 2018. https://www.uptodate.com/contents/epidemiology-and-classification-of-diabetic-neuropathy. Accessed January 29, 2020.
- Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al; National Fibromyalgia Guideline Advisory Panel. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. *Pain Res Manag.* 2013;18(3):119-126.
- Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomized, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain.* 2005;115:254-263.
- Galer B, Jensen M, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. *Clin J Pain*. 2002;18(5):297-301.
- Galer B, Rowbotham M, Perander J, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain.* 1999;80:533-538.
- Gilron I, Bailey RN, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324-1334.
- Goldenberg DL. Clinical manifestations and diagnosis of fibromyalgia in adults. Up To Date Web site. Updated August 10, 2019. www.uptodate.com. Accessed January 29, 2020.
- Goldenberg DL. Initial treatment of fibromyalgia in adults. UpToDate Web site. Updated November 6, 2018. www.uptodate.com. Accessed January 29, 2020.
- Gralise [package insert]. Depomed, Inc. Newark, CA. September 2015.
- Guan Y, Ding X, Cheng Y, et al. Efficacy of pregabalin for peripheral neuropathic pain: results of an eight-week, flexible-dose, double-blind, placebo-controlled study conducted in China. *Clin Ther*. 2011;33:159-166.
- Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guideline for developing a diabetes mellitus comprehensive care plan- 2015. *Endocr Pract.* 2015;21(Suppl 1):39-44.
- Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA*. 2009[a];301(2):198-209.
- Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin - a meta-analysis of randomized controlled trials. *Pain.* 2009[b];145(1-2):69-81.

- Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome (abstract). *J Pain*. 2010;11(6):505-521.
- Herndon CM, Strickland JM, Ray JB. Chapter 60. Pain Management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017.
- Horizant [package insert]. XenoPort, Inc. Santa Clara, CA. October 2016.
- Huffman CL, Goldenberg JN, Weintraub J, et al. Efficacy and safety of once-daily controlled-release pregabalin for the treatment of patients with postherpetic neuralgia: a double-blind, enriched enrollment randomized withdrawal, placebo-controlled trial. *Clin J Pain*. 2017;33(7):569-578. doi: 10.1097/AJP.0000000000000445.
- Ifuku M, Iseki M, Hidaka I, et al. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. *Pain Medicine.* 2011;12:1112-1126.
- Irving G, Backonja M, Rauck R, et al. NGX-4010, a Capsaicin 8% Dermal Patch, Administered Alone or in Combination With Systemic Neuropathic Pain Medications, Reduces Pain in Patients With Postherpetic Neuralgia. *Clin J Pain*. 2012;28(2):101-107.
- Irving G, Jensen M, Cramer M, et al. Efficacy and tolerability of gastric-retentive gabapentin for the treatment of postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial (abstract). *Clin J Pain*. 2009;25(3):185-192.
- Jensen MP, Chiang YK, Wu J. Assessment of pain quality in a clinical trial of gabapentin extended release for postherpetic neuralgia (abstract). *Clin J Pain*. 2009;25(4)286-292.
- Kajdasz DK, Iyengar S, Desaiah D, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther*. 2007;29:2536-2546.
- Katz N, Gammaitoni A, Davis MW, et al; Lidoderm Patch Study. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. *Pain Medicine.* 2002;3(4):324-332.
- Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. *Rheumatol Int*. 2016;36(5):663-672.
- Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy. *Neurology.* 2004;63:2104-2110.
- Lidoderm [package insert]. Endo Pharmaceuticals Inc. Malvern, PA. November 2018.
- Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;(1):CD007115.pub3.
- Lyrica [package insert]. Pfizer Inc. New York, NY. June 2019.
- Lyrica CR [package insert]. Pfizer Inc. New York, NY. June 2019.
- Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017 Feb;76(2):318-328. doi: 10.1136/annrheumdis-2016-209724.
- Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009;36:398-409.
- Mease PJ, Russell IJ, Kajdasz DK, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. *Semin Arthritis Rheum.* 2010;39:454-464.
- Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain.* 2003;106:151-158.
- Meng FY, Zhang LC, Liu Y, et al. Efficacy and safety of gabapentin for treatment of postherpetic neuralgia: a meta-analysis of randomized controlled trials. *Minerva Anesthesiol*. 2014;80(5):556-567.
- Moon DE, Lee DI, Lee SC, et al. Efficacy and tolerability of pregabalin using a flexible, optimized dose schedule in Korean patients with peripheral neuropathic pain: a 10-week, randomized, double-blind, placebo-controlled, multicenter study. *Clin Ther*. 2010;32:2370-2385.
- Neurontin [package insert]. Pfizer Inc. New York, NY. August 2019.
- Nucynta ER [package insert]. Janssen Pharmaceuticals, Inc. Titusville, NJ. October 2019.
- Ogawa S, Suzuki M, Arakawa A, et al. Long-term efficacy and safety of pregabalin in patients with postherpetic neuralgia: results of a 52-week, open-label, flexible-dose study (abstract). *Masui*. 2010;59(8):961-970.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm Accessed January 29, 2020.
- Parsons B, Li C. The efficacy of pregabalin in patients with moderate and severe pain due to diabetic peripheral neuropathy. *Curr Med Res Opin*. 2016;32(5):929-937.
- Pop-Busui R, Coulton A JM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154.
- Quilici S, Chancellor J, Lothgren M, et al. Meta-analysis of duloxetine vs pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol.* 2009;9:6-19.
- Qutenza [package insert]. Acorda Therapeutics, Inc. Ardsley, NY. August 2013.
- Raskin J, Smith TR, Wong K, et al. Duloxetine vs routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliative Med*. 2006;9(1):29-40.
- Rice ASC, Maton S; Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomized, double blind, placebo controlled study. *Pain.* 2001;94:215-24.
- Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain.* 2004;110:628-638.
- Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. *Clin Med Res & Opin*. 2010;26(10):2411-2419.
- Rowbotham M, Harden N, Stacey B, et al; Gabapentin Postherpetic Neuralgia Study Group. Gabapentin for the treatment of postherpetic neuralgia. A randomized controlled trial. *JAMA*. 1998;280:1837-1842.
- Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a six-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain.* 2008;136:432-444.

- Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomized, placebo-controlled clinical trial. *Pain.* 2004;109:26-35.
- Savella [package insert]. Forest Pharmaceuticals, Inc. New York, NY. December 2017.
- Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*. 2011;27(1):151-162
- Semel D, Murphy TK, Zlateva G, et al. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. *BMC Family Practice*. 2010;11:85.
- Sharma U, Griesing T, Emir B, et al. Time to onset of neuropathic pain reduction: a retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. *Am J Ther*. 2010;17:577-585.
- Siddall PJ, Cousins MJ, Otte A, et al. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology.* 2006 Nov 28;67(10):1792-1800.
- Skvarc NK, Kamenik M. Effects of pregabalin on acute herpetic pain and postherpetic neuralgia incidence. *Wien Klin Wochenschr*. 2010;122(Suppl 2):49-53.
- Tanenberg RJ, Clemow DB, Giaconia JM, et al. Duloxetine compared with pregabalin for diabetic peripheral neuropathic pain management in patients with suboptimal pain response to gabapentin and treated with or without antidepressants: a post hoc analysis. *Pain Pract.* 2014;14(7):640-648.
- Tanenberg RJ, Irving GA, Risser RC, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc*. 2011;86(7):615-24.
- Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? The “COMBO-DN study” – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain.* Dec 2013;154(12):2616-2625.
- Vinik AL, Perrot S, Vinik EJ, et al. Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: a randomised, 52-week, open-label, safety study. *BMC Neurol*. 2016;16(1):1-14.
- Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol Clin Exp*. 2004;19:S27-S35.
- Vranken JH, Kijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain.* 2008;136(1-2):150-157.
- Wallace MS, Irving G, Crowles VE. Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia: a randomized, double-blind, placebo-controlled, multicentre study (abstract). *Clin Drug Investig*. 2010;30(11):765-776.
- Welsch P, Uceyler N, Klose P, Walitt B, Hauser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev*. 2018;2:CD010292.
- Wernicke J, Lledo A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine. *Drug Safety*. 2007[a];30(5):437-455.
- Wernicke J, Wang F, Pritchett YL, et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Medicine.* 2007[b];8(6):503-513.
- Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;6:CD007938.
- Xochilcal-Morales M, Castro EM, Guajardo-Rosas J, et al. A prospective, open-label, multicentre study of pregabalin in the treatment of neuropathic pain in Latin America. *Int J Clin Pract.* 2010;64(9):1301-1309.
- Yan G, Guang N, Wei-ping J, et al. Duloxetine vs placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J*. 2010;123(22):3184-3192.
- Zhang L, Rainka M, Freeman R, et al. A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of gabapentin enacarbil in subjects with neuropathic pain associated with postherpetic neuralgia (PXN110748). *J Pain*. 2013;14(6):590-603.
- ZTlido [package insert]. Scilex Pharmaceuticals Inc. San Diego, CA. November 2018.

Publication Date: March 23, 2020

Prior Authorization Guideline

Guideline Name	Forteo (teriparatide injection)

1 . Indications

Drug Name: Forteo (teriparatide injection)
Postmenopausal women with osteoporosis at high risk of fracture Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Forteo reduces the risk of vertebral and nonvertebral fractures. **Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture** Indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. **Men and women with glucocorticoid-induced osteoporosis at high risk for fracture** Indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

2 . Criteria

Product Name: Forteo	
Diagnosis	Postmenopausal women with osteoporosis or osteopenia, or men with primary or hypogonadal osteoporosis or osteopenia at high risk for fracture
Approval Length	24 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of one of the following:

- Postmenopausal osteoporosis or osteopenia
- Glucocorticoid-induced osteoporosis
- Primary or hypogonadal osteoporosis or osteopenia

AND

2 – The recipient has a T score of ≤ 2.5

AND

3 – The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture

AND

4 – The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate, or the recipient has had esophagitis, or the recipient is unable to remain upright.

AND

5 – The recipient is not receiving any second line or third line osteoporosis therapy concurrently.

AND

6 – The total duration of treatment with this agent has not exceeded two years.

Prior Authorization Guideline

Guideline Name	Prolia (denosumab)

1 . Indications

Drug Name: Prolia (denosumab)
Treatment of postmenopausal women with osteoporosis at high risk for fracture Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. **Treatment to increase bone mass in men with osteoporosis at high risk for fracture** Indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. **Treatment of bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer** Indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures. NOTE: The use of Prolia for the treatment of bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer should not be confused with the use of Xgeva (another injectable formulation of denosumab) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors (including breast cancer and prostate cancer). **Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer** Indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. NOTE: The use of Prolia for the treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer should not be confused with the use of Xgeva (another injectable formulation of denosumab) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors (including breast cancer and prostate cancer). **Treatment of Glucocorticoid-Induced Osteoporosis** Indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either

initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

2 . Criteria

Product Name: Prolia	
Diagnosis	Postmenopausal Osteoporosis
Approval Length	12 months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 The recipient as a T score ≤ -2.5

AND

2 The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture.

AND

3 The recipient is not receiving any second line or third line osteoporosis therapy concurrently.

AND

4 The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

Product Name: Prolia	
Diagnosis	Male Osteoporosis
Approval Length	12 months

Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 The recipient as a T score ≤ -2.5

AND

2 The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture;

AND

3 The recipient is not receiving any second line or third line osteoporosis therapy concurrently;

AND

4 The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

Product Name: Prolia	
Diagnosis	Non-metastatic Prostate Cancer
Approval Length	12 months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture

AND

2 The recipient is receiving treatment with androgen-deprivation therapy(e.g., anti-androgen or luteinizing hormone-releasing hormone agents)

AND

3 The recipient is not receiving any second line or third line osteoporosis therapy concurrently

AND

4 The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright

Product Name: Prolia	
Diagnosis	Breast Cancer
Approval Length	12 months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture

AND

2 The recipient is receiving adjuvant aromatase inhibitor therapy (e.g.,anastrozole, exemestane and letrozole)

AND

3 The recipient is not receiving any second line or third line osteoporosis therapy concurrently

AND

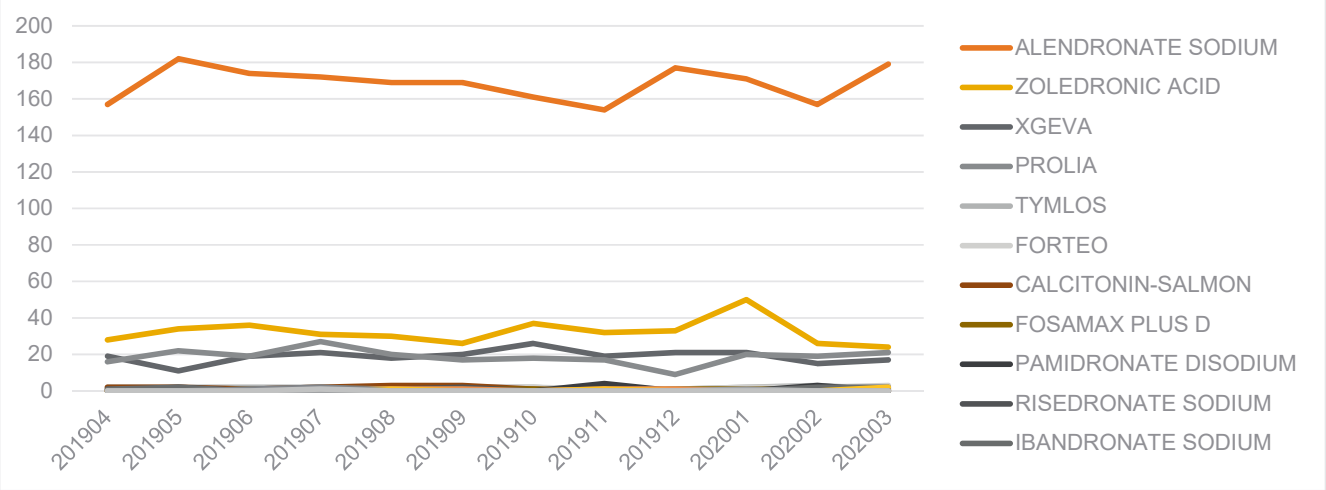
4 The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the

recipient is unable to remain upright.

Nevada Medicaid

Osteoporosis Agents
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Mem	Count of Claims	Total Days Supply	Total Quantity
BINOSTO	1	1	28	4
FORTEO	6	16	728	62
TYMLOS	5	20	648	33
FOSAMAX PLUS D	1	8	224	32
EVENITY	1	4	112	9
IBANDRONATE SODIUM	3	7	330	11
BONIVA	2	5	450	15
CALCITONIN-SALMON	6	15	450	56
ALENDRONATE SODIUM	512	2,022	88,198	14,610
RECLAST	1	1	1	1
XGEVA	56	227	254	383
ZOLEDRONIC ACID	165	387	387	7,333
RISEDRONATE SODIUM	4	8	398	47
PROLIA	158	225	2,779	229
ZOMETA	3	3	3	14
PAMIDRONATE DISODIUM	2	8	8	62
MIACALCIN	2	4	4	10



OO. Prolia® (Denosumab)

Therapeutic Class: Bone Resorption Inhibitors (Osteoporosis Agents)
Last Reviewed by DUR Board: October 25, 2012

Prolia® (Denosumab) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Postmenopausal Osteoporosis

1. The recipient has a T score $\leq$ -2.5; and

2. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture; and

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

b. Male Osteoporosis

1. The recipient has a T score $\leq$ -2.5; and

2. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture; and

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

c. Non-metastatic Prostate Cancer

1. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture;

2. The recipient is receiving treatment with androgen-deprivation therapy (e.g., anti-androgen or luteinizing hormone-releasing hormone agents);

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

d. Breast Cancer

1. The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture;

2. The recipient is receiving adjuvant aromatase inhibitor therapy (e.g., anastrozole, exemestane and letrozole);

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

PP. Forteo® (Teriparatide)

Therapeutic Class: Parathyroid/Bone Formation Stimulating Agent (Osteoporosis Agents)
Last Reviewed by DUR Board: October 25, 2012

Forteo® (Teriparatide) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. The recipient has been diagnosed with Postmenopausal Osteoporosis, or Glucocorticoid-Induced Osteoporosis, or the recipient is male and diagnosed with Primary or Hypogonadal Osteoporosis;

b. The recipient has a T score of $\leq$ 2.5;

c. The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture;

d. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate;

e. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

f. The total duration of treatment with this agent has not exceeded two years.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

Therapeutic Class Overview
Bone Density Regulators

INTRODUCTION

- Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture (*Cosman et al 2014*). The National Osteoporosis Foundation (NOF) estimated that in 2010, 12 million people in the United States had osteoporosis, and more than 2 million osteoporosis-related fractures occur annually, with more than 70% of these occurring in women. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (*Camacho et al 2016*).
- According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score (*World Health Organization 1994, 2007*).
- Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis, and low bone mass is the primary indicator of fracture risk (*Camacho et al 2016*). Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death (*Cosman et al 2014*).
- To decrease the risk of fractures, the general population should be advised to consume 1200 mg of calcium and 800 to 1000 mg of vitamin D per day from dietary sources or supplements. All individuals should also participate in regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Strategies for preventing falls should be implemented when needed. Smoking cessation and avoidance of excessive alcohol intake are other initiatives to prevent osteoporosis (*Camacho et al 2016, Cosman et al 2014*).
- Bisphosphonates are used to prevent and treat postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. There are several bisphosphonates approved for treatment of Paget's disease and malignancy-induced bone conditions, but not for osteoporosis. These agents include Aredia (pamidronate) zoledronic acid (Zometa) and Didronel (etidronate) (*Micromedex 2020*).
- Other agents used to treat osteoporosis include calcitonin (Miacalcin), an estrogen agonist/antagonist (Evista), the parathyroid hormone analogs (Forteo, Bonsity, and Tymlos), the receptor activator of nuclear factor K-B ligand inhibitor (Prolia), and the sclerostin inhibitor (Evenity). These agents also have other indications, such as: reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis; reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of Paget's disease; treatment of hypercalcemia; treatment of glucocorticoid-induced osteoporosis at high risk of fracture; treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer; and treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Another parathyroid hormone analog is Natpara, which is an injectable form of recombinant parathyroid hormone. Natpara is FDA approved for the treatment of hypocalcemia in patients with hypoparathyroidism as an adjunct to calcium and vitamin D supplementation *(Micromedex 2020)*.
- Other agents in the estrogen agonist/antagonist class include Clomid or Serophene (clomiphene), tamoxifen, Fareston (toremifene), and Osphena (ospemifene). These agents have different indications, including: to induce ovulation in appropriately selected anovulatory women desiring pregnancy; the treatment and prevention of breast cancer; and treatment of women experiencing moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause (*Micromedex 2020*). These agents will not be discussed in this review.
- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab (Prolia), is also available as Xgeva This product is approved to prevent skeletal-related events in patients with bone metastases from solid tumors, treat hypercalcemia of malignancy refractory to bisphosphonates, and treat adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (*Micromedex 2020*). It will not be further discussed in this review. The Food and Drug Administration (FDA) has approved estrogen/hormone therapy for the prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. The Women's Health Initiative (WHI) found that 5 years of hormone therapy in the form of Prempro (conjugated estrogen/medroxyprogesterone) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (*Writing Group for the WHI 2002*). However, the study also reported increased risks of myocardial infarction, stroke, invasive

breast cancer, pulmonary emboli, and deep vein thrombosis during 5 years of treatment. It is now recommended to use estrogen/hormone therapy in the lowest effective doses for the shortest duration necessary. Thus, these agents are not recommended for long-term prevention and will not be further discussed in this review.

- Medispan Class: Bone Density Regulators; Hormone Receptor Modulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bisphosphonates	
Actonel (risedronate)	✔
Atelvia (risedronate, delayed release tablet)	✔
Binosto (alendronate, effervescent tablet)	-
Boniva (ibandronate)	✔
Didronel (etidronate)*	✔
Fosamax (alendronate)	✔
Fosamax Plus D (alendronate/cholecalciferol)	-
Reclast (zoledronic acid)	✔
Calcitonin	
Miacalcin (calcitonin salmon) nasal solution*	✔
Estrogen Agonist-Antagonist	
Evista (raloxifene)	✔
Parathyroid Hormone Analogs	
Forteo, Bonsity (teriparatide)	-
Natpara (recombinant parathyroid hormone)**	-
Tymlos (abaloparatide)	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors	
Prolia (denosumab)	-
Sclerostin Inhibitor	
Evenity (romosozumab)	-

*Brand etidronate and calcitonin nasal spray are no longer marketed; products only available generically
**In September 2019, the manufacturer recalled this product due to concerns of the presence of rubber particulates. According to a January 21, 2020 update from the manufacturer, there is an expected delay of at least 1 year before the product becomes available in the US (*Takeda Pharmaceuticals 2020*).

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	alendronate* (Binosto, Fosamax, Fosamax Plus D)	etidronate (Didronel)	ibandronate* (Boniva)	risedronate* (Actonel, Atelvia)*	zoledronic acid* (Reclast)
Treatment of postmenopausal osteoporosis	✔		✔	✔	✔
Prevention of postmenopausal osteoporosis	✔ (Fosamax only)		✔ (tablets only)	✔ (Actonel only)	✔
Treatment to increase bone mass in men with osteoporosis	✔			✔ (Actonel only)	✔

Treatment of glucocorticoid-induced osteoporosis	✔ (Fosamax only)			✔ (Actonel only)	✔
Prevention of glucocorticoid-induced osteoporosis				✔ (Actonel only)	✔
Treatment of Paget's disease	✔ (Fosamax only)	✔		✔ (Actonel only)	✔
Treatment of heterotopic ossification due post hip replacement or spinal cord injury		✔			

* Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of Actonel, Reclast and Boniva (tablets) for the treatment of osteoporosis are based on clinical data of 3 years duration. The safety and effectiveness of Atelvia and Boniva injection for the treatment of osteoporosis are based on clinical data of 1 year duration. The safety and effectiveness of Binosto and Fosamax/Fosamax PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

(Prescribing information: Actonel 2019, alendronate solution 2019, Atelvia 2015, Binosto 2019, Boniva injection 2019, Boniva tablets 2016, etidronate 2017, Fosamax 2019, Fosamax Plus D 2019, Reclast 2017)

Table 3: FDA Approved Indications for Calcitonins, Estrogen Agonist-Antagonist, and Receptor Activator of Nuclear Factor K-B Ligand Inhibitor

Indication	Evista (raloxifene)	Evenity (romosozumab)	Miacalcin (calcitonin)	Prolia (denosumab)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause for whom alternative treatments are not suitable			✔	
Treatment of postmenopausal osteoporosis	✔			
Treatment of postmenopausal osteoporosis at high risk of fracture		✔		✔
Prevention of postmenopausal osteoporosis	✔			
Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis	✔			
Reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer	✔			
Treatment of Paget's disease			✔ (injection only)	
Treatment of hypercalcemia			✔ (injection only)	
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture				✔
Treatment to increase bone mass in men receiving androgen deprivation therapy for prostate cancer				✔
Treatment to increase bone mass in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✔
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✔
Treatment of osteoporosis in patients who have failed or are intolerant to other therapies		✔		

(*Prescribing Information: Calcitonin salmon nasal spray 2019, Evenity 2019, Evista 2019, Miacalcin injection 2018, Prolia 2019*)

Table 4: FDA Approved Indications for Parathyroid Hormone Analogs

Indication	Forteo, Bonsity (teriparatide)	Natpara (recombinant parathyroid hormone)	Tymlos (abaloparatide)
Adjunct to calcium and vitamin D for hypocalcemia due to hypoparathyroidism		✔	
Treatment of postmenopausal osteoporosis at high risk of fracture	✔		✔
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture	✔		
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture	✔		

(*Prescribing Information: Bonsity 2019, Forteo 2019, Natpara 2018, Tymlos 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Bisphosphonates

- Clinical trials for bisphosphonates included within this review evaluate their efficacy in increasing BMD and/or decreasing bone turnover markers (BTMs). Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD and reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focus on the same therapeutic outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.
- Head-to-head trials have resulted in conflicting data when comparing the efficacy among bisphosphonates.
  Data from trials and a meta-analysis specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk of developing fractures in both vertebral and nonvertebral areas, compared to placebo in both men and women (*Black et al 1996, Kanis et al 2005, Liu et al 2018, Lyles et al 2007, Ringe et al 2009, Sawka et al 2005*). Several meta-analyses have found that etidronate is effective for reducing the risk of vertebral fractures but not non-vertebral fractures when compared to placebo or calcium and vitamin D in postmenopausal women with osteoporosis (*Cranney et al 2001, Wells et al 2008).* Some evidence suggests that alendronate results in greater increases of BMD when compared to risedronate (*Bonnick et al 2006, Reid et al 2006, Reid et al 2008*). In an observational study, treatment with risedronate resulted in a greater reduction in the risk of nonvertebral and hip fractures compared to alendronate (*Silverman et al 2007*). In a small randomized trial (N = 50), once weekly alendronate demonstrated similar efficacy to daily risedronate (*Sarioglu et al 2006*). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over 1 year in a study with postmenopausal women with osteoporosis and over 2 years in a study of men with osteoporosis (*McClung et al 2007, Orwoll et al 2010*). Ibandronate was shown to reduce vertebral fractures more than alendronate and risedronate in 1 trial; however, 2 other trials demonstrated similar efficacy with ibandronate vs alendronate (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
  - Clinical trials have also established the efficacy of alendronate, risedronate, and zoledronic acid in patients with glucocorticoid-induced osteoporosis (*Mok et al 2008, Okada et al 2008, Reid et al 2009*). In a meta-analysis of 10 trials of alendronate in glucocorticoid-induced osteoporosis, the risk of fracture was not significantly affected despite significant improvements in BMD of the lumbar spine and femoral neck (*Wang et al 2018*). Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. One such trial demonstrated that zoledronic acid is more effective than risedronate for the treatment of Paget's disease (*Reid et al 2005*).

  - Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.
- In terms of safety, a meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events (AEs) concluded that patients treated with zoledronic acid had a higher probability of any GI AE and nausea. However, etidronate had the highest probability of discontinuation due to GI AEs compared to the other oral formulations, risedronate was associated with a greater incidence of serious GI AEs, and alendronate was associated with a greater incidence of upper GI and esophageal AEs. Ibandronate was not included in the analysis (*Tadrous et al 2014*).
- Alendronate effervescent tablets (Binosto) have been shown to be bioequivalent to alendronate tablets (Fosamax). Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week (*Binosto prescribing information 2016*).
- In a Phase 3 non-inferiority trial comparing oral ibandronate 100 mg to intravenous ibandronate 1 mg, both therapies led to comparable gains in BMD after 12 months in all evaluable subgroups (*Hagino et al 2018*).
- A systematic review evaluated the efficacy and safety of bisphosphonates in Paget's disease. The analysis included 20 studies (N = 3168). A total of 10 studies specifically compared bisphosphonates (etidronate, tiludronate, ibandronate, pamidronate, olpadronate, alendronate, risedronate, zoledronate) to placebo, and found that bisphosphonates tripled the proportion (31% vs 9%) of patients whose bone pain disappeared (risk ratio [RR], 1.97; 95% CI, 1.29 to 3.01). Results were similar across all bisphosphonates evaluated (*Corral-Gudino et al 2017*).
- The effectiveness of etidronate for the treatment of heterotopic ossification due post hip replacement or spinal cord injury has been demonstrated through several studies (*Banovac et al 1993, Banovac et al 2000, , Stover et al 1976[a], Stover et al 1976[b], Thomas et al 1985*).

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin; the body of evidence is primarily comprised of small observational trials (*Cadarette et al 2008, Chestnut et al 2000, Cranney et al 2002[b], Downs et al 2000, Hwang et al 2006, Kanis et al 1974, Woodhouse et al 1977*).
- Injectable calcitonin has demonstrated beneficial effects in the treatment of Paget's disease. Calcitonin therapy resulted in bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, calcitonin has been shown to cause disease regression in some patients (*kaufa et al 1974, Woodhouse et al 1977*).
- Nasal calcitonin achieved significant increases in BMD at the lumbar spine compared to placebo after 6 months of therapy, which was maintained for up to 2 years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement (*Chestnut et al 2000, Downs et al 2000*). Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonin significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for nonvertebral fractures (*Hwang et al 2006*).

Estrogen Agonist-Antagonist

- Several placebo-controlled trials have demonstrated that treatment with raloxifene in postmenopausal women with osteoporosis significantly increases BMD. In addition, raloxifene demonstrated beneficial effects on lipid profile parameters (*Eastell et al 2009, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Siris et al 2005, Tanaka et al 2011*). In the MORE trial, raloxifene decreased the risk of vertebral fractures compared to placebo, with no observed difference in the rate of nonvertebral fractures (*Kung et al 2003*). There was also no difference in nonvertebral fracture rate during a 7 year follow-up of the MORE trial (*Siris et al 2005*). These data are supported by results of a meta-analysis of seven placebo-controlled trials, in which the reduction in the risk of vertebral fractures associated with raloxifene was inconsistent between 2 clinical trials, and neither trial demonstrated a reduction in the risk in nonvertebral fractures (*Eastell et al 2009*). When compared to bisphosphonate therapy, increases in BMD were significantly greater with alendronate compared to raloxifene (*Recker et al 2007*).
- In addition to evaluating the efficacy of raloxifene on bone, the MORE trial evaluated its efficacy in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. As a secondary end point, raloxifene reduced the incidence of newly diagnosed invasive breast cancer compared to placebo (*Cummings et al 1999*). In addition, the CORE trial evaluated the efficacy of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of 8 years, the incidence of invasive breast cancer and estrogen receptor-positive breast cancer was reduced by 66% and 76%, respectively, with raloxifene compared to placebo. In the placebo-controlled RUTH trial, raloxifene significantly reduced the risk of invasive breast cancer, as well as vertebral fractures, and did not significantly

affect the risk of coronary heart disease. Raloxifene, however, was associated with a higher risk of venous thromboembolism and fatal stroke (*Barrett-Connor et al 2006*).

- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the 2 treatments (*Vogel et al 2006*). However, in a trial with a median follow-up of 6.75 years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years (*Vogel et al 2010*).
- In terms of safety data, raloxifene was most commonly associated with hot flashes and leg cramps. Several clinical trials reported thromboembolic events (*Bachmann et al 2011, Barrett-Conner et al 2006, Cadarette et al 2008, Cranney et al 2002[a], Cummings et al 1999, Eastell et al 2009, Ensrud et al 2006, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Martino et al 2004, Recker et al 2007, Siris et al 2005, Tanaka et al 2011, Vogel et al 2006, Vogel et al 2010*).

Parathyroid Hormone Analogs

- A 2-year, placebo-controlled trial (N = 437) evaluating teriparatide in increasing bone mass in men with primary or hypogonadal osteoporosis was terminated early when a long-term toxicology trial noted an increase in the incidence of osteosarcoma in rats receiving teriparatide. After a median duration of 11 months, teriparatide significantly increased BMD at the lumbar spine and femoral neck compared to placebo (*Orwoll et al 2003*). In a follow-up of this trial, no serious safety concerns with teriparatide were observed (*Kaufman et al 2005*). Teriparatide has been compared to the bisphosphonate alendronate for the treatment of men with primary or hypogonadal osteoporosis. Specifically, when compared to alendronate and the combination of teriparatide plus alendronate, teriparatide significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (*Finkelstein et al 2003*).
- Teriparatide also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. Additionally, significantly fewer patients receiving teriparatide had a vertebral fracture after 36 months (*Langdahl et al 2009, Saag et al 2007, Saag et al 2009*). Teriparatide was also compared to risedronate in men with glucocorticoid-induced osteoporosis. At 18 months, teriparatide was more effective at increasing BMD at the lumbar spine than risedronate (*Gluer et al 2013*).
- Teriparatide has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Hwang et al 2006, Kendler et al 2018, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Yuan et al 2019*). The double-blind, double-dummy, multicenter, randomized, controlled VERO trial enrolled 1360 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T score ≤ -1.50 (*Kendler et al 2018*). Patients were randomly assigned to receive 20 mcg of teriparatide once daily plus oral weekly placebo or 35 mg risedronate once weekly plus daily placebo injections for 24 months. The primary outcome was new radiographic vertebral fractures. Results revealed that new vertebral fractures occurred in 28 (5.4%) patients in the teriparatide group and 64 (12%) patients in the risedronate group (risk ratio, 0.44; 95% confidence interval [CI], 0.29 to 0.68; $p < 0.001$). Clinical fractures were also significantly reduced with teriparatide (4.8% vs 9.8%; $p = 0.0009$). The EUROFORS trial was a prospective, 2-year trial in which all patients received teriparatide for the first year of treatment. After 12 months, patients were divided into 2 substudies. In Substudy 1, for the second year of treatment, patients were randomized to teriparatide, the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on teriparatide for the second year of treatment. After the first year of treatment, teriparatide significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of teriparatide appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued teriparatide for a total of 2 years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of treatment, BMD at the lumbar spine, total hip, and femoral neck continued to increase significantly with teriparatide. BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significantly increased BMD at the femoral neck (*Eastell et al 2009, Minne et al 2008, Obermayer-Pietsch et al 2008*). In addition to significant increases in BMD, placebo-controlled trials demonstrate that teriparatide significantly reduces the risk of vertebral and nonvertebral fractures (*Body et al 2002, Lindsay et al 2004, Neer et al 2001*). Data also suggest that teriparatide in combination with a

bisphosphonate may result in significant increases in BMD compared to monotherapy with either teriparatide or a bisphosphonate (*Cosman et al 2009, Cosman et al 2011*). In another study of 12 months duration, combined teriparatide plus denosumab were compared to either treatment alone. Combination therapy was associated with significantly greater BMD increases at the posterior-anterior spine, femoral neck, and hip than either drug alone (*Leder et al 2014, Tsai et al 2013*).

- A systematic review and meta-analysis of 23 RCTs examining upper limb and hip fractures found a significant reduction in hip fractures with teriparatide compared to either placebo or other medications (odds ratio [OR], 0.44; 95% CI, 0.22 to 0.87; p=0.019); however, no difference was seen in reduction of humerus, forearm, or wrist fractures *(Diez-Perez et al 2019)*. A second systematic review of 17 studies showed that teriparatide reduced vertebral and nonvertebral fractures when compared to placebo but did not reduce wrist and hip fractures *(Chen et al 2019)*. Additionally, there was no difference in fracture risk reduction between teriparatide and other medications.
- In terms of safety data, no clinically significant concerns related to teriparatide were observed; however, treatment was associated with a higher rate of hypercalcemia compared to placebo and bisphosphonate therapy. No cases of osteosarcoma were reported (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Finkelstein et al 2003, Finkelstein et al 2006, Hwang et al 2006, Kaufman et al 2005, Langdahl et al 2009, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Orwoll et al 2003, Saag et al 2007, Saag et al 2009*).
- The efficacy of abaloparatide was compared with teriparatide and placebo in the 18-month randomized controlled ACTIVE trial in 2463 postmenopausal women with osteoporosis. Treatment with abaloparatide resulted in a significant reduction in new morphometric vertebral and nonvertebral fractures vs placebo, while treatment with teriparatide also resulted in a significant reduction in new morphometric vertebral fractures vs placebo. For reduction in nonvertebral fractures, treatment with abaloparatide was not statistically different from teriparatide. The incidence of hypercalcemia was significantly lower with abaloparatide vs teriparatide (*Miller et al 2016*). The ACTIVExtend open-label extension trial evaluated 6 months of follow-up therapy with alendronate 70 mg once weekly in both the abaloparatide and placebo groups, and demonstrated that the treatment cycle with abaloparatide for 18 months followed by alendronate reduced new morphometric vertebral fractures by 87%, nonvertebral fractures by 52%, clinical fractures by 45%, and major osteoporotic fractures by 58% vs placebo and alendronate (*Cosman et al 2017*).
- Several RCTs have examined the effect of recombinant parathyroid hormone on BMD. In 2 RCTs, recombinant parathyroid hormone significantly increased BMD at 12 and 18 months in postmenopausal women with osteoporosis compared to placebo; however, 1 of these RCTs found a decrease in BMD at the forearm at 18 months *(Greenspan et al 2007, Hodsman et al 2003).* There are several studies examining the effect of recombinant parathyroid hormone on BMD in patients with hypoparathyroidism, but these studies generally include small sample sizes or lack a comparator arm. Results have been inconsistent in showing an increase in BMD, and 2 of these studies have shown a decrease in BMD at the hip, spine, whole body, or radius *(Cusano et al 2013, Rubin et al 2016, Sikjaer et al 2011).*

Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

- The safety and efficacy of denosumab for the treatment of bone loss in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer were established in a 2 year, double-blind, placebo-controlled, randomized trial enrolling 252 women (*Ellis et al 2008*). Patients were randomized to subcutaneous denosumab every 6 months (n = 127) or placebo (n = 125) for a total of 4 doses; all patients received supplemental calcium and vitamin D. Overall, denosumab increased BMD at the lumbar spine at 12 and 24 months by 5.5% and 7.6%, respectively, compared to placebo ($p < 0.0001$ at both time points). BMD at the lumbar spine was significantly higher with denosumab compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95% CI, 4.8 to 6.3; $p < 0.0001$). Furthermore, after 2 years, denosumab increased BMD at the lumbar spine (-1.4% placebo, +4.8% denosumab), total hip (-1.0% placebo, +3.8% denosumab), and femoral neck (-0.8% placebo, +2.8% denosumab).
- A double-blind, placebo-controlled, Phase 3 trial evaluated denosumab vs placebo in 3420 postmenopausal women with early hormone-receptor positive breast cancer receiving treatment with aromatase inhibitors (*Gnant et al 2015*). Women were randomized to denosumab 60 mg every 6 months or placebo. The primary outcome measure of time to first fracture was significantly delayed in the denosumab group compared to placebo (hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.65; $p < 0.0001$). The incidence of AEs was similar in both treatment groups.
- When compared to placebo, denosumab significantly prolonged bone-metastasis-free survival (composite of time to first occurrence of bone metastasis and death from any cause) in men with non-metastatic prostate cancer (treatment difference, 4.2 months; HR, 0.85; 95% CI, 0.73 to 0.98; p = 0.028). There was no difference in overall survival observed

between the 2 treatment groups. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with denosumab compared to placebo ($p < 0.001$ for all). Of note, the FDA-approved dosing was not evaluated in this trial; denosumab was administered once monthly (*Smith et al 2012*). The ADAMO trial showed that denosumab therapy administered every 6 months continued to increase BMD in men with low BMD throughout the second year of treatment (*Langdahl et al 2015*).

- Of the available clinical trial data evaluating the safety and efficacy of denosumab in postmenopausal women with osteoporosis who are at high risk of fracture, only one placebo-controlled trial (the FREEDOM trial) demonstrated a reduction in the risk of fracture with denosumab. In this trial, after 36 months, there were significant reductions with denosumab compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk [RR], 0.32; 95% CI, 0.26 to 0.41; $p < 0.001$), nonvertebral (6.5% vs 8%; RR, 0.80; 95% CI, 0.67 to 0.95; $p = 0.01$), and hip fractures (0.7% vs 1.29%; RR, 0.6; 95% CI, 0.31 to 0.97; $p = 0.04$) (*Cummings et al 2009*). A 3-year extension trial maintained patients randomized to denosumab on active treatment for a total of 6 years and crossed over the placebo patients to denosumab treatment for a total of 3 years. For patients on denosumab for 6 years, BTMs were maintained at lower than pretreatment levels and BMD continued to increase. Fracture incidence in the long-term group remained low and below the rates reported in the FREEDOM placebo group. For the cross-over group, data obtained were consistent with FREEDOM observations (ie, rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, favorable benefit/risk profile) (*Bone et al 2013*). A 7-year extension of FREEDOM, for a total of 7 to 10 years of exposure to denosumab, further confirmed a low fracture incidence rate with low rates of AEs (*Bone et al 2017*). Additionally, BMD at the lumbar spine, total hip, femoral neck, and radius continued to increase, suggesting no plateau to BMD benefits with denosumab.
- A meta-analysis/systematic review of clinical trials of denosumab in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of denosumab on BTMs and BMD. In this analysis, AEs, including fracture risk, were also evaluated as secondary endpoints. Due to missing or unavailable data, it was not possible for the investigators to evaluate the efficacy of denosumab based on change in baseline BMD. Treatment with denosumab was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, denosumab did not demonstrate a significant reduction in fracture risk (OR, 0.74; 95% CI, 0.33 to 0.64; $p = 0.45$) (*Anastaskilakis et al 2009*).
- The efficacy of denosumab for increasing BMD is also supported by 3 dose-ranging, placebo-controlled trials, as well as a head-to-head trial with the bisphosphonate, alendronate (*Brown et al 2009, Lewiecki et al 2007, McClung et al 2006, Miller et al 2008[b]*). The 3 dose-ranging trials demonstrated that 48 months of denosumab therapy significantly increased BMD at all measured skeletal sites (lumbar spine, total hip, and distal 1/3 radius) ($p < 0.001$), and achieved potent and sustained reductions of BTMs compared to placebo (*Cummings et al 2009*). In a small subset of patients who discontinued treatment with denosumab, subsequent decreases in BMD at measured skeletal sites were observed. When compared to alendronate, changes in BMD at the total hip were also significantly greater with denosumab at 12 months (3.5% vs 2.6%; $p < 0.0001$) (*Brown et al 2009*). In a second meta-analysis comparing denosumab to weekly alendronate, no difference in fracture risk was demonstrated (OR, 1.42; 95% CI, 0.84 to 2.40; $p = 0.19$); however, both treatments were associated with significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after 6 months (*Lin et al 2012*). In a 12-month trial comparing denosumab to monthly ibandronate therapy, treatment with denosumab resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate (*Recknor et al 2013*).
- A systematic review and meta-analysis assessed the efficacy and safety of denosumab compared to other anti-osteoporosis agents (eg, bisphosphonates, teriparatide) in patients previously treated with other medications (*Fontalis et al 2018*). Results demonstrated the superiority of denosumab in augmenting BMD at all skeletal sites studied (treatment difference in total hip [primary outcome], 1.59%; 95% CI, 1.01 to 2.17) compared to controls, whereas the overall incidence of serious AEs was not increased ($p = 0.42$). Similar results were demonstrated in another meta-analysis comparing denosumab to bisphosphonates for the treatment of postmenopausal osteoporosis. In this analysis, denosumab significantly increased the change in total hip, femoral neck, and lumbar spine BMD when compared to bisphosphonates. Denosumab did not yield any increased benefit for reducing fracture risk when compared to bisphosphonates and both denosumab and bisphosphate therapy demonstrated a similar incidence of AEs and withdrawals due to AEs (*Wu et al 2018*).
- The impact of denosumab compared to risedronate on BMD was evaluated in 795 patients with glucocorticoid-induced osteoporosis. At 24 months, the increase in lumbar spine and total hip BMD was significantly higher with denosumab compared to risedronate in patients on glucocorticoids for less than 3 months (mean percentage change: 4.5% for the

lumbar spine, 3.1% for the total hip, and 2.5% for the femoral neck) as well as for those taking glucocorticoids for greater than 3 months (mean percentage change: 3.2% for the lumbar spine, 2.5% for the total hip, and 1.8% for the femoral neck). The incidence of discontinuation of treatment due to AEs was 7.9% with denosumab and 9.6% with risedronate. Fractures were reported in 8.8% in the denosumab group (4.4% vertebral, 5.3% non-vertebral) and 9.1% of patients taking risedronate (6.9% vertebral, 3.8% non-vertebral). The incidence of infection was approximately 36% in both groups (*Saag et al 2019*).

- A systematic review and meta-analysis assessed the effect of denosumab vs bisphosphonate treatment on BMD, fractures and safety in patients with glucocorticoid-induced osteoporosis . Collective data from 3 clinical trials demonstrated that one year of denosumab therapy increased lumbar (2.32%, 95% CI, 1.73% to 2.91%, p<0.0001) and hip (1.52%, 95% CI, 1.1% to 1.94%, p<0.0001) BMD more than bisphosphonates . The analysis found similar rates of fracture incidence, AEs and, infection between both treatments (*Yanbeiy and Hansen 2019).*
- In terms of safety data, no clinically significant concerns related to denosumab were observed; the safety profile of denosumab appears similar to that of bisphosphonates (*Anastaskilakis et al 2009, Brown et al 2009, Cummings et al 2009, Lewiecki et al 2007, Lin et al 2012, McClung et al 2006, Miller et al 2008[b], Smith et al 2012*).

Sclerostin Inhibitors

- The efficacy of romosozumab in postmenopausal women with osteoporosis was demonstrated in 2 clinical trials. When compared with placebo, romosozumab significantly decreased vertebral and clinical fractures; however, there was no statistically significant difference in nonvertebral fractures between patients receiving placebo or romosozumab *(Cosman et al 2016)*. In a trial comparing 24 months of alendronate with 12 months of romosozumab followed by 12 months of alendronate, a significant reduction in new vertebral fracture risk was observed in the romosozumab treatment group at 24 months. Additionally, patients receiving romosozumab followed by alendronate had a lower risk of new vertebral fracture, clinical fracture, hip fracture, and nonvertebral fracture, which was significant compared to the alendronate only group *(Saag et al 2017)*.
- An RCT examining the use of romosozumab in men > 50 years of age with osteoporosis and a history of fragility fracture showed a significant increase in BMD at the spine and hip compared to placebo *(Lewiecki et al 2018).*

Comparative Efficacy

- From the Agency for Healthcare Research and Quality (AHRQ) evaluation (*Crandall et al 2012*), the following conclusions were reached:
  - Calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis.
  - There is a high level of evidence from randomized controlled trials (RCTs) that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
  - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
  - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.
  - There is insufficient evidence from head-to-head trials with bisphosphonates to support the superiority of one agent over the others for the prevention of fractures.
  - The evidence is insufficient regarding the use of combination therapy or sequential use of osteoporosis therapies in relation to fracture outcomes.
  - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men.
  - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies.
  - About half of patients appeared to show persistence with osteoporosis treatment at 1 year.
  - Adverse effects of concern identified from the report included the following:
    - A relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
    - Evidence is high for an increased risk for venous thromboembolic events (eg, pulmonary embolism) and vasomotor symptoms (eg, hot flashes) with raloxifene therapy.
    - Evidence is insufficient regarding the risk of esophageal cancer with bisphosphonates.

  - Evidence is high regarding the risk for alendronate and mild upper GI events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn).
  - Evidence is high that the prevention and treatment of osteoporosis with bisphosphonates remains a relatively minor contributor to the development of osteonecrosis of the jaw.
  - The risk remains low for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis compared with the numbers of osteoporotic fractures prevented by bisphosphonate therapy.
  - Evidence is high for rashes, injection site reactions, and infection with denosumab.
  - A 2016 surveillance report of the document summarized new evidence with respect to AEs that were not reported in the original report. (*Agency for Healthcare Research and Qualilty 2016*). These include risk of:
    - Cerebrovascular accident, myocardial infarction, GI events, death, arrhythmia, dyspnea, and hypertension with teriparatide.
    - Headache, dizziness, arthritis/arthralgia, and hypotension with raloxifene.
    - Dermatological conditions and falls with denosumab.
- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In 2 clinical trials, bisphosphonate and parathyroid hormone analog therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon (*Downs et al 2000, Hwang et al 2006*).
- A network meta-analysis found that zoledronic acid significantly increased BMD in lumbar spine and teriparatide decreased fracture rates in men with osteoporosis when compared to other agents such as alendronate, ibandronate, and risedronate (*Chen et al 2015*).
- A network meta-analysis performed indirect comparisons to determine the likelihood of each drug being the most preferable for various outcomes (*Yang et al 2016*). Among products included in this study, the most preferred agents for various outcomes were teriparatide in nonvertebral fractures; denosumab, zoledronic acid, and alendronate in hip fractures; teriparatide in wrist fractures; and raloxifene, alendronate, and denosumab for AEs.
- A systematic review and meta-analysis demonstrated teriparatide to be superior to alendronate in increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the change from baseline in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the 2 therapies (*Wang et al 2017[a]*).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of 3 RCTs to evaluate the comparative safety and efficacy of teriparatide, abaloparatide, and zoledronic acid for treatment of osteoporosis in postmenopausal women at high risk for fracture The analysis determined that teriparatide and abaloparatide were not significantly different from each other or zoledronic acid in reducing morphometric vertebral or nonvertebral fractures, and safety issues had little influence on the net benefit for each therapy compared to each other (*CTAF 2017*).
- A systematic review and meta-analysis demonstrated significantly lower risk of vertebral fractures with alendronate and risedronate in men with osteoporosis, but not with injectable calcitonin or denosumab vs controls. For bisphosphonates as a treatment category, meta-analyses demonstrated a significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (*Nayak et al 2017*).
- A network meta-analysis identified parathyroid hormone therapy (teriparatide) and zoledronic acid as agents with the highest probability of satisfactory performance in preventing vertebral fractures in postmenopausal women in the final relative ranking of interventions among 10 osteoporosis agents, including oral bisphosphonates, denosumab, raloxifene, and strontium ranelate. For prevention of clinical vertebral fractures, zoledronic acid was determined to be the most effective, with denosumab as a second option, when compared to placebo. There were no significant differences between therapies identified with respect to adverse effects (*Wang et al 2017[b]*).
- A prospective cohort study of 32 patients with glucocorticoid-induced osteoporosis found that denosumab 60 mg subcutaneously every 6 months was superior to alendronate 35 mg orally once weekly in increasing lumbar spine BMD at 12 months ($p < 0.05$) (*Iseri et al 2018*).
- A systematic review of 6 RCTs found significant improvement in bone strength in postmenopausal women with osteoporosis receiving denosumab compared to bisphosphonates at 12 months in 4 of the 6 studies; however, bone turnover marker was consistently lower in patients receiving denosumab (*Chandran et al 2019)*
- A systematic review and meta-analysis of 16 trials (N=18,940) evaluated the impact of bone anabolic therapies (teriparatide, abaloparatide, romosozumab) compared to bisphosphonates or placebo on fractures (primary outcome), BMD, and bone markers in patients with postmenopausal osteoporosis. Abaloparatide ranked better than other active

treatments for reduction in vertebral and non-vertebral fractures. For the secondary outcome of increase in BMD, romosozumab ranked highest for all BMD locations compared to other active treatments. Compared to other treatments, teriparatide had the greatest impact on bone formation markers. However, about 30% of the trials in this analysis were found to have a high risk of bias (*Hernandez 2019*).

CLINICAL GUIDELINES

- To prevent and/or treat osteoporosis in postmenopausal women and men, national guidelines recommend adequate calcium and vitamin D intake, weight bearing exercise, cessation of smoking, and limiting alcohol intake (*ACOG 2012 [reaffirmed in 2019], Adler et al 2016, Buckley et al 2017, Camacho et al 2016, Conley 2020, Cosman et al 2014, Eastell et al 2019, Qaseem et al 2017, Watts et al 2012*).
- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Eastell et al 2019, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*).
  - Bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another. Because etidronate is not approved for the indication of prevention or treatment of osteoporosis, many guidelines do not recommend its use *(ACOG 2012, Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Qaseem et al 2017, Watts et al 2012)*.
  - While some national guidelines recommend denosumab as an alternative to bisphosphonates (*ACOG 2012, Eastell et al 2019*), the American Association of Clinical Endocrinologists (AACE) recommends denosumab as an optional first-line treatment in postmenopausal women (*Camacho et al 2016*).
  - Teriparatide is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). The Endocrine society has recommended abaloparatide or teriparatide as treatment options in postmenopausal women at very high risk of fracture (*Eastell et al 2019).*
  - Although calcitonin and raloxifene are approved for osteoporosis, they are not considered first-line therapies due to AEs, less evidence of efficacy, and/or route of administration.
  - A recent guideline from the American Society for Bone and Mineral Research (ASBMR) specifically geared toward secondary fracture prevention in patients 65 years of age and older recommends the following for pharmacologic therapy (*Conley et al 2020*):
    - Oral alendronate or risedronate as first-line treatment (considered well-tolerated and available at a low cost). Intravenous zoledronic acid or subcutaneous denosumab are recommended if oral bisphosphonates cannot be used.
    - Patients at high-risk (specifically after vertebral fractures): consider anabolic therapies in consultation with a specialist.
    - Optimal duration of treatment is unknown but general recommendation is 3 to 5 years due to potential risk of rare adverse events that increase with longer duration of treatment.
    - Consider risks and monitor for atypical femoral fractures and osteonecrosis of the jaw.
- Patients with chronic kidney disease (CKD) grades 3a to 3b with parathyroid hormone in the normal range and osteoporosis and/or high risk of fracture should receive treatment similar to that of the general population (*Ketteler et al 2018*).
- According to the Endocrine Society guideline for Paget's disease, treatment with bisphosphonates is recommended for most patients with active or symptomatic Paget's disease who are at risk of future complications. A single 5 mg dose of intravenous zoledronic acid is recommended as the preferred initial agent in patients with no contraindications (*Singer et al 2014*).

SAFETY SUMMARY

- **Contraindications**
  - Bisphosphonates
    - Oral agents: Abnormalities of the esophagus that delay esophageal emptying (eg, stricture or achalasia)
    - Oral agents: Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate)
    - Hypocalcemia
    - Clinically overt osteomalacia (etidronate)

- Creatinine clearance <35 mL/min or acute renal impairment (zoledronic acid)
  - Alendronate oral solution
    - Patients at increased risk of aspiration
  - Raloxifene
    - Active or past history of venous thromboembolism
    - Pregnancy or nursing mothers
  - Denosumab
    - Hypocalcemia
    - Pregnancy or nursing mothers
  - Romosozumab
    - Hypocalcemia

- **Warnings/precautions**
  - Bisphosphonates
    - Caution should be used in patients with active GI problems (except zoledronic acid)
    - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
    - Osteonecrosis of the jaw
    - Caution should be used in aspirin-sensitive patients (zoledronic acid)
    - Caution should be used in patients who must restrict sodium intake (alendronate effervescent tablets)
    - Hypocalcemia must be corrected prior to use
    - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
    - Patients receiving Atelvia should not be treated with Actonel, as both products contain the same active ingredient
    - Renal toxicity may occur in patients with pre-existing renal impairment receiving ibandronate injection
  - Raloxifene
    - **Boxed warning:** Increased risk of venous thromboembolism and death from stroke
    - Venous thromboembolism: increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue 72 hours prior to and during prolonged immobilization
    - Death due to stroke
    - Should not be used for the primary or secondary prevention of cardiovascular disease
    - Not recommended in premenopausal women
    - Caution should be used in patients with hepatic impairment
    - Concomitant use with systemic estrogens is not recommended
    - Hypertriglyceridemia; serum triglycerides should be monitored throughout treatment for women with a history of marked hypertriglyceridemia receiving treatment with raloxifene and oral estrogen or estrogen plus progestin
  - Parathyroid Hormone Analogs
    - **Boxed warning:** Parathyroid hormone analogs should not be used in patients at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, prior external beam or implant radiation involving the skeleton, and in pediatric and young adult patients with open epiphyses)
      - Cumulative lifetime use of abaloparatide and/or teriparatide > 2 years not recommended
      - Recombinant parathyroid hormone should only be used in patients that are unable to be controlled on calcium and vitamin D
    - Orthostatic hypotension
    - Caution should be used in patients with active or recent urolithiasis
    - Hypercalcemia
    - Hypocalcemia following discontinuation of recombinant parathyroid hormone
  - Calcitonin
    - Potential increased risk of malignancies
    - Circulating antibodies and abnormal urine sediment
    - Hypocalcemia
    - Nasal spray: Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur
  - Denosumab

- Atypical, low-energy, or low trauma fractures of the femoral shaft
- Osteonecrosis of the jaw
- Severe musculoskeletal pain
- An increased risk for multiple vertebral fractures has been reported following discontinuation of denosumab
- Increased risk for serious infections in patients on concomitant immunosuppressant agents or with impaired immune systems
- Patients receiving Prolia should not be treated with Xgeva, as both products contain the same active ingredient
- Hypersensitivity reactions, including anaphylaxis, may occur
- Hypocalcemia must be corrected prior to use. Concomitant use of calcium-lowering drugs or calcimimetic drugs may increase risk of hypocalcemia.
- Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
- Dermatologic reactions, including dermatitis, rash, and eczema have been reported, and may require discontinuation of the drug
- Significant suppression of bone remodeling may occur and may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing

  - Romosozumab
    - **Boxed warning:** There may be an increase in risk of myocardial infarction, stroke, and cardiovascular death. Romosozumab should not be used in patients with a stroke or myocardial infarction within the past year and should be discontinued if events occur during therapy.
    - Major adverse cardiac events may occur
    - Hypersensitivity reactions may occur
    - Hypocalcemia must be corrected prior to use
    - Osteonecrosis of the jaw
    - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
    - Use should be limited to 12 monthly doses

- **AEs**
  - Bisphosphonates
    - The most common AEs are headache and GI effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.
  - Raloxifene
    - The most common AEs (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating.
  - Teriparatide
    - The most common AEs (> 10%) include nausea, arthralgia, and pain.
  - Abaloparatide
    - The most common AEs (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.
  - Recombinant parathyroid hormone
    - The most common AEs (> 10%) include paresthesia, hypocalcemia, headache, hypercalcemia, hypoaesthesia, diarrhea, vomiting, arthralgia, nausea, hypercalciuria, and extremity pain.
  - Calcitonin
    - Nasal spray: The most common AEs (≥ 3%) include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
    - Injection: The most common AEs include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).
  - Denosumab
    - The most common AEs (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, cystitis, nasopharyngitis, bronchitis, and headache. Pancreatitis has also been reported in clinical trials.
  - Romosozumab
    - The most common AEs (≥ 5%) include arthralgia and headache.

- **Drug Interactions**
  - Bisphosphonates

- Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with absorption of oral bisphosphonates
- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) increase GI AEs with oral bisphosphonates
- Olestra, mineral oils, orlistat and bile acid sequestrants may impair the absorption of vitamin D (alendronate/cholecalciferol).

○ Raloxifene
- Cholestyramine, warfarin, highly protein-bound drugs, ampicillin, and amoxicillin.

○ Teriparatide and recombinant parathyroid hormone
- Hypercalcemia may predispose patients to digitalis toxicity; caution recommended in patients on digoxin

○ Calcitonin
- Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations

- **Risk Evaluation and Mitigation Strategy (REMS)**
  - ○ Denosumab has a REMS program with the goal of mitigating the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions (*REMS Website 2020*).
    - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe denosumab.
  - ○ Recombinant parathyroid hormone has a REMS program with the goal of increasing awareness and mitigating the risk of osteosarcoma *(REMS Website 2020).*
    - All prescribers and dispensing pharmacies must be certified through the REMS program.

DOSING AND ADMINISTRATION

- Bisphosphonates
  - ○ Oral bisphosphonates should be taken at least 30 minutes (60 minutes for ibandronate) before the first food or drink of the day and swallowed whole in an upright position and with a full glass of plain water. Patients should not lie down for 30 minutes (60 minutes for ibandronate) after ingestion.
    - Exception: Delayed-release risedronate should be taken immediately after breakfast
  - ○ Supplemental calcium and vitamin D are recommended if dietary intake is inadequate; however, calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with bisphosphonate absorption and should be administered at a different time of the day.
- Calcitonin
  - ○ Unopened nasal spray bottle should be stored in the refrigerator. Once opened, it should be stored at room temperature and discarded after 35 days.
  - ○ Injection should be stored in the refrigerator. If the volume of the injection exceeds 2 mL, intramuscular (IM) injection is preferable, and the total dose should be distributed across multiple injection sites.
- Parathyroid Hormone Analogs
  - ○ Teriparatide prefilled pens should be refrigerated at all times and injected into the thigh or abdominal wall.
  - ○ Abaloparatide prefilled pens should be refrigerated before use then stored at room temperature for up to 30 days after first use. The injection should be into the periumbilical region of abdomen at approximately the same time every day.
  - ○ Recombinant parathyroid hormone must be reconstituted prior to administration using a mixing device and should be administered using the Q-Cliq pen delivery device into the thigh, rotating thighs each day. Reconstituted parathyroid hormone should be stored in the Q-Cliq pen device in the refrigerator for no more than 14 days.
- Denosumab
  - ○ Denosumab should be administered by a healthcare professional in the upper arm, upper thigh, or abdomen.
- Romosozumab
  - ○ Romosozumab should be administered by a healthcare professional as 2 separate injections, one after the other in the upper arm, thigh, or abdomen.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Bisphosphonates			

Drug	Available Formulations	Route	Usual Recommended Frequency
Actonel (risedronate)	Tablets	Oral	Once daily Once weekly Once monthly
Atelvia (risedronate)	Delayed release tablets	Oral	Once weekly
Binosto (alendronate)	Effervescent tablets	Oral	Once weekly
Boniva (ibandronate)	Tablets Injection	Oral IV	Once monthly (oral) Every 3 months (IV)
Didronel (etidronate)	Tablets	Oral	Once daily (for osteoporosis and Paget's disease)
Fosamax (alendronate)	Tablets Solution	Oral	Once daily Once weekly
Fosamax Plus D (alendronate/ cholecalciferol)	Tablets	Oral	Once weekly
Reclast (zoledronic acid)	Injection	IV	Once a year (treatment) Once every 2 years (prevention)
Calcitonin			
Miacalcin (calcitonin-salmon synthetic)	Nasal solution Injection	Intranasal SQ, IM	Once daily (for osteoporosis and Paget's disease)
Estrogen Agonist-Antagonist			
Evista (raloxifene)	Tablets	Oral	Once daily
Parathyroid Hormone Analogs			
Forteo, Bonsity (teriparatide)	Injection	SQ	Once daily
Natpara (recombinant parathyroid hormone)	Injection	SQ	Once daily
Tymlos (abaloparatide)	Injection	SQ	Once daily
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
Prolia (denosumab)	Injection	SQ	Every 6 months
Sclerostin Inhibitor			
Evenity (romosozumab)	Injection	SQ	Once monthly

Abbreviations: IM = intramuscular; IV = intravenous; SQ = subcutaneous

See the current prescribing information for full details

CONCLUSION

- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Conley et al 2020, Cosman et al 2014, Eastell et al 2019, Ketteler et al, 2018, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*). Bisphosphonates are generally considered first-line therapy, and clinical trials have not consistently shown one agent to be more effective than another.
- Data for hip, vertebral, and nonvertebral fractures are most robust for alendronate, risedronate, and zoledronic acid. Ibandronate has data to support reduced vertebral fractures (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
- Patient preference and ease of administration should be considered in the selection of a bisphosphonate, as adherence may be a barrier to the treatment and prevention of osteoporosis. Atelvia (risedronate delayed release) and alendronate can be administered once weekly, while Actonel (risedronate) and ibandronate can be administered once a month. Additionally, zoledronic acid is an intravenous infusion given once a year for treatment or every other year for prevention. Atelvia (risedronate delayed release) can be taken immediately after eating or drinking while other oral bisphosphonates must be administered 30 to 60 minutes before the first food or drink of the day.

- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab, has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. Monitoring for infection is required with this agent. The AACE recommends denosumab as an optional first-line treatment for postmenopausal osteoporosis (*Camacho et al 2016*) or as an option for patients who cannot take oral bisphosphonates (*Conley et al 2020*)
- Teriparatide and abaloparatide are generally reserved for patients at high risk for fractures (*Conley et al 2020*) or those unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). Both teriparatide and abaloparatide are administered via daily subcutaneous injection, and lifetime cumulative treatment duration should not exceed 2 years. The parathyroid hormone analogs have a boxed warning for osteosarcoma.
- Romosozumab is the newest agent approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture and in patients who have failed or are intolerant to other therapies, and it has not yet been incorporated into treatment guidelines. It is administered as a monthly subcutaneous injection for no more than 12 months.
- Raloxifene has data for vertebral fracture reduction and is only approved for women. It may be an appropriate initial therapy for patients requiring drugs with spine-specific efficacy who are unable to tolerate bisphosphonates (*Camacho et al 2016*). Raloxifene is also used for breast cancer risk reduction, which is recommended for asymptomatic women ≥ 35 years of age who are at risk for breast cancer. There is an increased risk of thromboembolism and stroke with raloxifene.
- The ASBMR 2020 guideline mentions anabolic therapy such as romosozumab as an option in patients at high risk of secondary fracture; particularly those with a previous vertebral fracture (Conley et al 2020).
- Calcitonin lacks sufficient evidence for fracture reduction in the treatment of osteoporosis.
- For the treatment of Paget's disease, risedronate, alendronate, etidronate, calcitonin injection, and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, teriparatide, alendronate, denosumab, and zoledronic acid are all FDA-approved. Selection of an agent should be based on the patient's preference of administration. Oral bisphosphonates are preferred. If these cannot be used, the agents recommended in order of preference are IV bisphosphonates, teriparatide, and then denosumab (*Buckley et al 2017*).

REFERENCES

- Actonel prescribing information. Allergan USA, Inc. Irvine, CA. November 2019.
- Adler RA, Fuleihan GE, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a task force of the American society for bone and mineral research. *J Bone & Miner Res*. 2016;31(1):16-35.
- Agency for Healthcare Research and Quality. AHRQ Systematic Review Surveillance Program. August 2016.. https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/osteoporosis-bone-fracture_surveillance.pdf. Accessed February 10, 2020.
- Alendronate sodium solution prescribing information. TAGI Pharma. South Beloit, IL. September 2019.
- American College of Obstetricians and Gynecologists (ACOG). Practice bulletin 129: Osteoporosis. *Obstetrics & Gynecology*. 2012;120(3):718-734.
- Anastaskilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. *Horm Metab Res*. 2009;41:721-729.
- Atelvia prescribing information. Warner Chilcott. Rockaway, NJ. April 2015.
- Bachmann G, Kriegman A, Goncalves J, et al. Effect of zoledronic acid compared to raloxifene on bone turnover markers in postmenopausal women with low bone density. *Menopause*. 2011;18(8):851-856.
- Banovac K, Gonzalez F, Wade N, et al. Intravenous disodium etidronate therapy in spinal cord injury patients with heterotopic ossification. *Paraplegia*. 1993; 31:660-666.
- Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury. *J Spinal Cord Med*. 2000; 12(1):40-44.
- Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355(2):125-137.
- Binosto prescribing information. ASCEND Therapeutics. Herndon, VA. October 2019.
- Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-41.
- Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2002 Oct;87(10):4528-35.
- Bone HG, Chapuriat R, Brandi ML, et al. The effect of 3 or 6 years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin Endocrin Metab*. 2013;98(11):4483-4492.
- Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5(7):513-523.
- Boniva injection prescribing information. Genentech USA, Inc. South San Francisco, CA. April 2019.
- Boniva tablets prescribing information. Genentech USA, Inc. South San Francisco, CA. December 2016.
- Bonnick S, Saag KG, Kiel DP, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate vs risedronate over two years. *J Clin Endocrinol Metab*. 2006;91:2631-2637.

- Bonsity prescribing information. Pfenex, Inc. San Diego, CA. October 2019.
- Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009;24:153-161.
- Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017;69(8):1521-1537.
- Cadarette SM, Katz JN, Brookhart A, et al. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med*. 2008;148:637-646.
- Calcitonin salmon nasal spray prescribing information. Par Pharmaceutical, Inc. Chestnut Ridge, NY. March 2019.
- California Technology Assessment Forum (CTAF). Anabolic therapies for osteoporosis in postmenopausal women: effectiveness and value (evidence report). 2017. https://icer-review.org/wp-content/uploads/2016/11/CTAF_Osteoporosis_Evidence_Report_061617.pdf. Accessed February 10, 2020.
- Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016. *Endocr Pract*. 2016;22(Suppl 4):1-42.
- Chandran T, Venkatachalam I. Efficacy and safety of denosumab compared to bisphosphonates in improving bone strength in postmenopausal osteoporosis: a systematic review. *Singapore Med J.* 2019;60(7):364-378.
- Chen LX, Zhou ZR, Li YL, et al. Comparison of Bone Mineral Density in Lumbar Spine and Fracture Rate among Eight Drugs in Treatments of Osteoporosis in Men: A Network Meta-Analysis. *PLoS ONE*. 2015;10(5):e0128032.
- Chen Y, Liu R, Hettinghouse A, Wang S, et al. Clinical application of teriparatide in fracture prevention: a systematic review. *JBJS Rev.* 2019;7(1):e10.
- Chestnut CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med*. 2000;109(4):267-276.
- Conley RB, Adib G, Adler RA, et al. Secondary fracture prevention: consensus clinical recommendations for a multistakeholder coalition. *J Bone & Miner Res.* 2020;35(1):36-52. doi: 10.1002/jbmr.3877.
- Corral-Gudino L, Tan AJ, Del Pino-Montes J et al. Bisphosphonates for Paget's disease of bone in adults. *Cochrane Database Syst Rev*. 2017;12(12):CD004956.
- Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543.
- Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014; 25(10): 2359–2381.
- Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26(3):503-511.
- Cosman F, Miller PD, Williams GC, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. *Mayo Clin Proc*. 2017;92(2):200-210.
- Cosman R, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresportive agent. *J Clin Endrocinol Metab*. 2009;94:3772-3780.
- Crandall CJ, Newberry SJ, Gellad WG, et al. Treatment to prevent fractures in men and women with low bone density or osteoporosis: update of a 2007 report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No. HHSA-290-2007-10062-I.) Rockville, MD: Agency for Healthcare Research and Quality; March 2012. Surveillance report: August 2016. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/osteoporosis-bone-fracture_surveillance.pdf. Accessed February 10, 2020.
- Cranney A, Guyatt G, Krolicki N, et al; Osteoporosis Research Advisory Group. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int.* 2001;12(2):140-51.
- Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev*. 2002[a];23(4):524-528.
- Cranney A, Tugwell P, Zytaruk N, et al; Osteoporosis Methodology Group and Osteoporosis Research Advisory Group. Meta-analysis of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. *Endoc Rev*. 2002[b];23(4):540-551.
- Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA*. 1999;281(23):2189-2197.
- Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.
- Cusano NE, Rubin MR, McMahon DJ, et al. Therapy of hypoparathyroidism with PTH(1-84): a prospective four-year investigation of efficacy and safety. *J Clin Endocrinol Metab.* 2013;98(1):137-144.
- Diez-Perez A, Marin F, Eriksen EF, et al. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: a systematic review and meta-analysis. *Bone*. 2019;120:1-8.
- Downs RW JR, Bell NH, Ettinger MP, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *J Clin Endocrinol Metab*. 2000;85(5):1783-1788.
- Drugs@FDA. FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 5, 2020.
- Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled, European Study of Forteo (EUROFORS). *J Bone Miner Res*. 2009;24:726-736.
- Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104(5):1595-1622.
- Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromastase inhibitors for nonmetastatic breast cancer. *J Clin Oncol*. 2008;26(30):4875-4882.
- Ensrud K, Genazzani AR, Geiger MJ, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol*. 2006;97:520-527.
- Etidronate disodium prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV. March 2017.
- Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a three-year randomized clinical trial. *JAMA*. 1999;282(7):637-624.
- Evenity prescribing information. Amgen Inc. Thousand Oaks, CA. December 2019.

- Evista prescribing information. Lilly USA, LLC. Indianapolis, IN. December 2019.
- Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med*. 2003;349(13):1216-1226.
- Finkelstein JS, Leder BZ, Burnett SM, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. *J Clin Endocrinol Metab*. 2006;91(8):2882-287.
- Fontalis A, Kenanidis E, Prousali E, Potoupnis M, Tsiridis E. Safety and efficacy of denosumab in osteoporotic patients previously treated with other medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2018;17(4):413-428. doi: 10.1080/14740338.2018.1430764.
- Food and Drug Administration (FDA). Approved Risk Evaluation and Mitigation Strategies (REMS). Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed February 10, 2020.
- Forteo prescribing information. Lilly USA, LLC. Indianapolis, IN. October 2019.
- Fosamax PLUS D prescribing information. Merck and Co., Inc. Whitehouse Stations, NJ. August 2019.
- Fosamax prescribing information. Merck and Co., Inc. Whitehouse Station, NJ. August 2019.
- Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res*. 2013;28(6):1355-1368.
- Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2015 Aug 1;386(9992):433-43. doi: 10.1016/S0140-6736(15)60995-3.
- Greenspan SL, Bone HG, Ettinger MP, et al; Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med.* 2007;146(5):326-339.
- Guanabens N, Monegal A, Cerda D, et al. Randomized Trial Comparing Monthly Ibandronate and Weekly Alendronate for Osteoporosis in Patients With Primary Biliary Cirrhosis. *Hepatology*. 2013;58(6):2070-208.
- Hagino H, Ito M, Hashimoto J, et al. Monthly oral ibandronate 100 mg is as effective as monthly intravenous ibandronate 1 mg in patients with various pathologies in the MOVEST study. *J Bone Miner Metab.* 2018;36(3):336-343. doi: 10.1007/s00774-017-0839-2.
- Harris ST, Reginster JY, Harley C, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the evaluation of ibandronate efficacy (VIBE) database fracture study. *Bone*. 2009;44:758-765.
- Hernandez AV, Perez-Lopez FR, Piscoya A, et al. Comparative efficacy of bone anabolic therapies in women with postmenopausal osteoporosis: a systematic review and network meta-analysis of randomized controlled trials. *Maturitas.* 2019; 129:12-22. doi: 10.1016/j.maturitas.2019.08.003.
- Hodsman AB, Hanley DA, Ettinger MP, et al. Efficacy and safety of human parathyroid hormone-(1-84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab.* 2003;88(11):5212-5220.
- Hwang JS, Tu ST, Yang TS, et al. Teriparatide vs calcitonin in the treatment of Asian postmenopausal women with established osteoporosis. *Osteoporos Int.* 2006;17:373-378.
- Iseri K, Iyoda M, Watanabe M, et al. The effects of denosumab and alendronate on glucocorticoid-induced osteoporosis in patients with glomerular disease: A randomized, controlled trial. *PLoS One*. 2018;13(3):e0193846. doi: 10.1371/journal.pone.0193846.
- Johnston Jr CC, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women. *Arch Intern Med*. 2000;160:3444-3450.
- Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. *Osteoporos Int.* 2005;16:475-482.
- Kanis JA, Horn DB, Scott RDM, Strong JA. Treatment of Paget's disease of bone with synthetic salmon calcitonin. *Br Med J*. 1974;3:727-731.
- Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int.* 2005;16:510-516.
- Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicenter, double-blind, double-dummy, randomized controlled trial. *Lancet*. 2018;391(10117):230-240. doi: 10.1016/S0140-6736(17)32137-2.
- Ketteler M, Block GA, Evenepoel P, et al. Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder: Synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. *Ann Intern Med.* 2018;168(6):422-430. doi: 10.7326/M17-2640.
- Kung AWC, Chao HT, Huang KE, et al. Efficacy and safety of raloxifene 60 mg/day in postmenopausal Asian women. *J Clin Endocrinol Metab*. 2003;88:3130-136.
- Langdahl BL, Marin F, Shane E, et al. Teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. *Osteoporos Int.* 2009;20(12):2095-2104.
- Langdahl BL, Teglbjaerg CS, Ho P, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. *J Clin Endocrinol Metab*. 2015;100:1335–1342.
- Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA extension study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99:1694-1700.
- Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab.* 2018;103(9):3183-3193.
- Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res*. 2007;22:1832-1841.
- Lin T, Wang C, Cai XZ, et al. Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. *Int J Clin Pract*. 2012;66(4):399-408.
- Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med*. 2004;164:2024-2030.
- Liu GF, Wang ZQ, Liu L, Zhang BT, Miao YY, Yu SN. A network meta-analysis on the short-term efficacy and adverse events of different anti osteoporosis drugs for the treatment of postmenopausal osteoporosis. *J Cell Biochem*. 2018;119(6):4469-4481. doi: 10.1002/jcb.26550.

- Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357:1799-1809.
- Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004;96(23):1751-1761.
- McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*. 2007;41:122-128.
- McClung MR, Lewiecki M, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354:821-831.
- McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med*. 2005;165:1762-1768.
- Miacalcin injection prescribing information. Mylan Institutional LLC. Rockford, IL. July 2018.
- Micromedex [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2020. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed February 5, 2020.
- Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008[b];43:222-229.
- Miller PD, Epstein S, Sedarati F, Reginster JY. Once-monthly oral ibandronate compared to weekly oral alendronate in postmenopausal osteoporosis: results from the heat-to-head MOTION study. *Curr Med Res Opin*. 2008[a];24(1):207-213.
- Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722-733.
- Minne H, Audrah M, Simones ME, et al. Bone density after teriparatide in patients with or without antiresportive treatment: one-year results from the EUROFORS study. *Curr Med Res Opin*. 2008;24(11):3117-3128.
- Mok CC, Tong KH, To CH, et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. *Osteoporos Int.* 2008;19:357-364.
- Natpara prescribing information. Shire-NPS Pharmaceuticals, Inc. Lexington, MA. December 2018.
- Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2017 Mar;65(3):490-495.
- Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434-1441.
- North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*. 2010;17(1):25-54.
- Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresportive treatment. *J Bone Miner Res*. 2008;23(10):1591-1600
- Okada Y, Nawata M, Nakayamada S, et al. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. *J Rheumatol*. 2008;35:2249-2254.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 5, 2020.
- Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg vs a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res*. 2010;25(10):2239-2350.
- Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis (abstract). *J Bone Miner Res*. 2003;18(1):9-17.
- Prolia prescribing information. Amgen, Inc. Thousand Oaks, CA. July 2019.
- Qaseem A, Forciea MA, McLean RM, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(11):818-839.
- Recker RR, Kendler D, Recknor CP, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone*. 2007;40:843-851.
- Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol.* 2013;121(6):1291-1299.
- Reclast prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. July 2017.
- Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicenter, double-blind, double-dummy, randomized controlled trial. *Lancet*. 2009;373:1253-1263.
- Reid DM, Hosking D, Kendler D, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-international. *Int J Clin Pract*. 2008;62(4):575-584.
- Reid DM, Hosking D, Kendler D, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: results of FACTS-International. *Clin Drug Invest.* 2006;26(2):63-74.
- Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med*. 2005;353(9):898-908.
- Ringe JD, Farahman P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. *Rheumatol Int.* 2009;29:311-315.
- Rubin MR, Cusano NE, Fan WW, et al. Therapy of hypoparathyroidism with PTH (1-84): A prospective six year investigation of efficacy and safety. *J Clin Endocrinol Metab.* 2016;101(7):2742-2750.
- Saag KG, Pannacciulli N, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: final results of a twenty-four-month, randomized, double-blind, double-dummy trial. *Arthritis Rheumatol*. 2019;71(7):1174-1184. doi: 10.1002/art.40874.
- Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med.* 2017;377(15):1417-1427.

- Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007;357(20):2028-2039.
- Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis. Thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum.* 2009;60(11):3346-3355.
- Sarioglu M, Tuzum C, Unlu Z, et al. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in postmenopausal osteoporosis. *Rheumatol Int.* 2006;26:195-200.
- Sawka AM, Papaioannou A, Adachi JD, et al. Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. *BMC Musculoskelet Disord*. 2005;6:39.
- Sikjaer T, Rejnmark L, Rolighed L, et al; for the Hypoparathyroid Study Group. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. *J Bone Miner Res.* 2011;26(10):2358-2370.
- Silverman SL, Watts NB, Delmas PD, et al. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporos Int.* 2007;18:25-34.
- Singer FR, Bone HG, Hosking DJ, et al. Paget's disease of bone: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(12):4408-22.
- Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after eight years: results from the continuing outcomes relevant to Evista (CORE) study. *J Bone Miner Res*. 2005;20(9):1514-1524.
- Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379:39-46.
- Stover SL, Hahn HR, Miller JM. Disodium etidronate in the prevention of heterotopic ossification following spinal cord injury (preliminary report). *Paraplegia* 1976[a];14(2):146-56.
- Stover SL, Neimann KM, Miller JM. Disodium etidronate in the prevention of postoperative recurrence of heterotopic ossification in spinal-cord injury patients. *J Bone Join Surg Am*. 1976[b];58(5):683-8.
- Tadrous M, Wong L, Mamdani MM, et al. Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. *Osteoporos Int.* 2014;25:1225-1235.
- Takeda Pharmaceuticals. Update on timing of Natpara availability in the US. January 21, 2020. https://www.takeda.com/en-us/newsroom/natpara-updates/ Accessed February 5, 2020.
- Tanaka M, Itoh K, Matsushita K, et al. Effects of raloxifene on bone mineral metabolism in postmenopausal Japanese women on hemodialysis. *Ther Apher Dial*. 2011 Jun;15(Suppl 1):S62-S6.
- Thomas BJ, Amstutz HC. Results of the administration of diphosphonate for the prevention of heterotopic ossification after total hip arthroplasty. *J Bone Join Surg Am*. 1985; 67(3):400-403.
- Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;382: 50–56.
- Tymlos prescribing information. Radius Health, Inc. Waltham, MA. October 2018.
- Vogel VG, Constantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727-2741.
- Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer. *Cancer Prev Res (Phila).* 2010;3(6):696-706.
- Wang G, Sui L, Gai P, et al. The efficacy and safety of vertebral fracture prevention therapies in postmenopausal osteoporosis treatment: Which therapies work best? A network meta-analysis. *Bone Joint Res*. 2017[b];6(7):452-463.
- Wang YK, Qin SQ, Ma T, et al. Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017[a];96(21):e6970.
- Wang YK, Zhang YM, Qin SQ, et al. Effects of alendronate for treatment of glucocorticoid-induced osteoporosis: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018;97(42):e12691. doi: 10.1097/MD.0000000000012691.
- Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: An endocrine society clinical practice guideline. *J Clin Endocrin Metab*. 2012; 97(6):1802–1822.
- Wells GA, Cranney A, Peterson J, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev.* 2008;(1):CD003376. doi: 10.1002/14651858.CD003376.pub3.
- Woodhouse NJY, Chalmers AH, Wells IP, et al. Paget's disease. Radiological changes occurring in untreated patients and those on therapy with salmon calcitonin during two years' observation. *Br J Radiol*. 1977;50(598):699-705.
- World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Geneva, World Health Organization, 1994 (WHO technical report series, No. 843).
- World Health Organization. WHO scientific group on the assessment of osteoporosis at primary health care level. Geneva, World Health Organization, 2007.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288(3):321-333.
- Wu J, Zhang Q, Yan G, Jin X. Denosumab compared to bisphosphonates to treat postmenopausal osteoporosis: a meta-analysis. *J Orthop Surg Res*. 2018;13(1):194. doi: 10.1186/s13018-018-0865-3.
- Yanbeiy ZA and Hansen KE. Denosumab in the Treatment of Glucocorticoid-Induced Osteoporosis: A Systematic Review and Meta-Analysis. *Drug Des Devel Ther*. 2019;13:2843-2852.
- Yang XC, Deng ZH, Wen T, et al. Network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. *Cell Physiol Biochem*. 2016;40(3-4):781-795.
- Yuan F, Peng W, Yang C, Zheng J. Teriparatide versus bisphosphonates for treatment of postmenopausal osteoporosis: a meta-analysis. *Int J Surg.* 2019;66:1-11.

Publication Date: February 19, 2020

Prior Authorization Guideline

Guideline Name	PCSK9 Inhibitors

1 . Criteria

Product Name: Praluent*	
Approval Length	6 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following diagnosis:

1.1 The patient has a diagnosis of heterozygous familial hypercholesterolemia (HeFH)

OR

1.2 The patient has a diagnosis of clinical atherosclerotic cardiovascular disease and requires additional lowering of LDL-C (defined as acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin)

AND

2 - The patient is 18 years of age or older

AND

3 - The requested medication is being prescribed by or in consultation with a cardiologist or lipid specialist

AND

4 - The requested medication will be used as an adjunct to a low-fat diet and exercise regimen

AND

5 - One of the following

5.1 The patient has a labeled contraindication to all statins documented in their medical record (the contraindication must be provided and documented)

OR

5.2 All of the following:

5.2.1 The patient has received high intensity statin therapy, defined as atorvastatin (Lipitor) ≥40 mg or rosuvastatin (Crestor) ≥20 mg for at least the past 3 months

AND

5.2.2 One of the following:

5.2.2.1 The patient received add-on therapy with ezetimibe (Zetia) in combination with high or moderate intensity statin therapy for at least the past two weeks

OR

5.2.2.2 The patient has a contraindication to ezetimibe (Zetia) therapy

AND

5.2.3 The patient's LDL-C after therapy for at least the past 3 months ≥100 mg/dL (diagnosis of heterozygous familial hypercholesterolemia) or ≥ 70 mg/dL (diagnosis of clinical atherosclerotic cardiovascular disease)

AND

5.2.4 The patient will continue the prescribed statin regimen in combination with PCSK9 therapy

OR

5.3 All of the following:

5.3.1 The patient has a contraindication or intolerance to high intensity statin therapy

AND

5.3.2 The patient received therapy with one of the following statins for at least the past 3 months:

- atorvastatin (10 to 20 mg)
- rosuvastatin (5 to 10 mg)
- simvastatin (>20 mg)
- pravastatin (>40 mg)
- lovastatin (40 mg)
- fluvastatin (40 mg twice daily)
- fluvastatin ER (80 mg)
- pitavastatin (>2 mg)

AND

5.3.3 One of the following:

5.3.3.1 The patient received add-on therapy with ezetimibe (Zetia) in combination with high or moderate intensity statin therapy for at least the past two weeks

OR

5.3.3.2 The patient has a contraindication to ezetimibe (Zetia) therapy

AND

5.3.4 The patient's LDL-C after therapy for at least the past 3 months ≥100 mg/dL (diagnosis of heterozygous familial hypercholesterolemia) or ≥ 70 mg/dL (diagnosis of clinical atherosclerotic cardiovascular disease)

AND

5.3.5 The patient will continue the prescribed statin regimen in combination with PCSK9 therapy

OR

5.4 The patient experienced an adverse reaction to at least 2 statins that are documented in the member's medical record

AND

6 - The request does not exceed the quantity limit established by Nevada Medicaid

Product Name: Praluent*	
Approval Length	1 Year
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The patient has been adherent with PCSK9 inhibitor therapy

AND

2 - One of the following:

2.1 The patient is currently receiving statin therapy in combination with PCSK9 inhibitor

OR

2.2 The patient has a labeled contraindication to statin therapy (contraindication must be provided and documented)

AND

3 - The patient achieved a reduction in LDL-C level

Product Name: Repatha, Repatha SureClick, Repatha PushTronex *	
Approval Length	6 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following:

1.1 The patient is 18 years of age or older and has a diagnosis of Heterozygous familial hypercholesterolemia (HeFH)

OR

1.2 The patient is 18 years of age or older and has a diagnosis of Clinical atherosclerotic cardiovascular disease and requires additional lowering of LDL-C (defined as acute coronary syndromes, history of myocardial Infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin)

OR

1.3 The patient is 13 years of age or older and has a diagnosis of homozygous familial hypercholesterolemia (HoFH)

AND

2 - The requested medication is being prescribed by or in consultation with a cardiologist or lipid specialist

AND

3 - The requested medication will be used as an adjunct to a low-fat diet and exercise regimen

AND

4 - One of the following:

4.1 The patient has a labeled contraindication to all statins documented in their medical record (the contraindication must be provided and documented)

OR

4.2 All of the following:

4.2.1 The patient has received high intensity statin therapy, defined as atorvastatin (Lipitor) ≥40 mg or rosuvastatin (Crestor) ≥20 mg for at least the past 3 months

AND

4.2.2 One of the following:

4.2.2.1 The patient received add-on therapy with ezetimibe (Zetia) in combination with high or moderate intensity statin therapy for at least the past two weeks

OR

4.2.2.2 The patient has a contraindication to ezetimibe (Zetia) therapy

AND

4.2.3 The patient's LDL-C after therapy for at least the past 3 months ≥100 mg/dL (diagnosis of heterozygous familial hypercholesterolemia) or ≥ 70 mg/dL (diagnosis of clinical atherosclerotic cardiovascular disease)

AND

4.2.4 The patient will continue the prescribed statin regimen in combination with PCSK9 therapy

OR

4.3 All of the following:

4.3.1 The patient has a contraindication or intolerance to high intensity statin therapy

AND

4.3.2 The patient received therapy with one of the following statins for at least the past 3 months:

- atorvastatin (10 to 20 mg)
- rosuvastatin (5 to 10 mg)
- simvastatin (>20 mg)
- pravastatin (>40 mg)
- lovastatin (40 mg)
- fluvastatin (40 mg twice daily)
- fluvastatin ER (80 mg)
- pitavastatin (>2 mg)

AND

4.3.3 One of the following:

4.3.3.1 The patient received add-on therapy with ezetimibe (Zetia) in combination with high or moderate intensity statin therapy for at least the past two weeks

OR

4.3.3.2 The patient has a contraindication to ezetimibe (Zetia) therapy

AND

4.3.4 The patient's LDL-C after therapy for at least the past 3 months ≥100 mg/dL (diagnosis of heterozygous familial hypercholesterolemia) or ≥ 70 mg/dL (diagnosis of clinical atherosclerotic cardiovascular disease

AND

4.3.5 The patient will continue the prescribed statin regimen in combination with PCSK9 therapy

OR

4.4 The patient experienced an adverse reaction to at least 2 statins that are documented in the member's medical record

AND

5 - The request does not exceed the quantity limit established by Nevada Medicaid

Product Name: Repatha, Repatha SureClick, Repatha PushTronex *	
Approval Length	1 Year
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The patient has been adherent with PCSK9 inhibitor therapy

AND

2 - One of the following:

2.1 The patient is currently receiving statin therapy in combination with PCSK9 inhibitor

OR

2.2 The patient has a labeled contraindication to statin therapy (contraindication must be provided and documented)

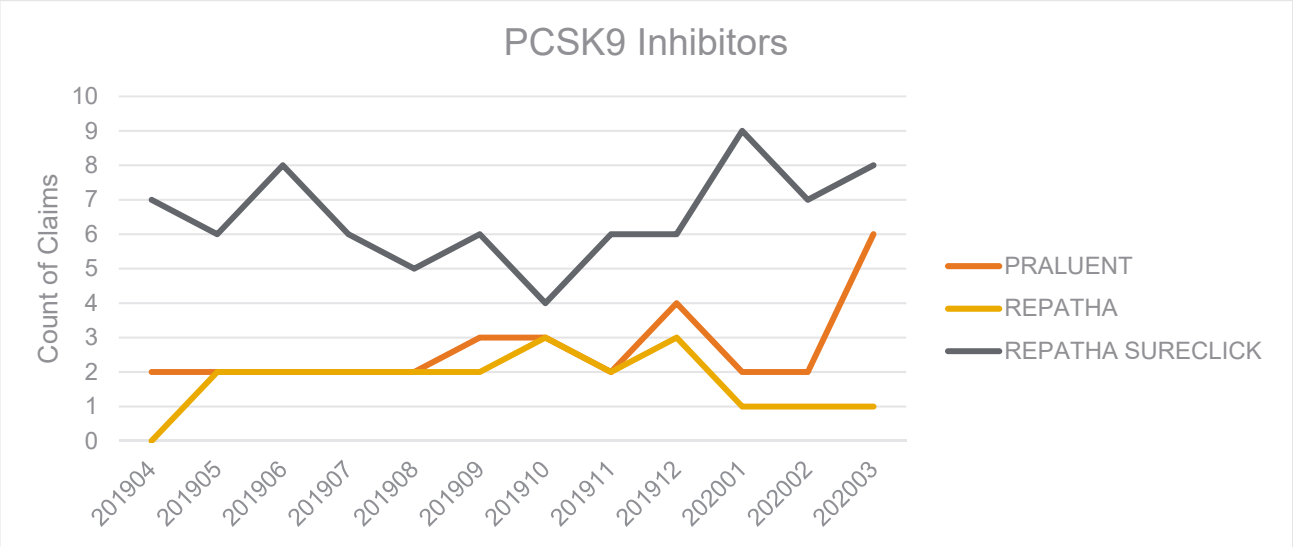
AND

3 - The patient achieved a reduction in LDL-C level

Nevada Medicaid

PCSK9 Inhibitors
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Men	Count of Claims	Total Days Supply	Total Quantity
REPATHA	2	21	532	38
PRALUENT	4	32	896	64
REPATHA SURECLICK	15	78	2,222	156



EEE. Anti-lipidemic Agents – PCSK9 Inhibitors

Therapeutic Class: Antilepemic Agent, PCSK9 Inhibitors
Last Reviewed by the DUR Board: January 28, 2016

Anti-lipidemic Agents – PCSK9 Inhibitors are subject to prior authorization and quantity limitation based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if all the following criteria are met and documented:

a. Initial Request:

1. The recipient has an FDA-approved diagnosis; and

2. The requested medication was prescribed by or in consultation with a cardiologist or lipid specialist; and

3. The requested medication will be used as an adjunct to a low-fat diet and exercise; and

4. For the treatment of homozygous familial hypercholesterolemia:

a. With alirocumab (Praluent®)

1. The recipient is 18 years of age or older; or

b. With evolocumab (Repatha®)

1. The recipient is 13 years of age or older.

5. And the recipient must meet one of the following (a, b, c, or d):

a. The recipient has had an inadequate response to high intensity statin therapy defined as all of the following:

1. The recipient has received therapy with atorvastatin $\geq$ 40 mg or rosuvastatin $\geq$ 20 mg for at least the past three months; and

2. The recipient has received add-on therapy with ezetimibe to the maximum tolerable dose of statin for at least the past two weeks or the recipient has a contraindication to ezetimibe therapy; and

3. The LDL-C after therapy for at least the past three months was ≥ 100 mg/dL (HeFH) for ≥ 70 mg/dL (clinical atherosclerotic cardiovascular disease); and

4. The statin therapy will be continued with PCSK-9 therapy.

b. Or, the recipient has had an inadequate response to moderate intensity statin therapy defined as all of the following:

1. The recipient has an intolerance or contraindication to high intensity statin therapy; and

2. The recipient has received therapy with:

a. atorvastatin 10 to 20 mg; or

b. rosuvastatin 5 to 10 mg; or

c. simvastatin > 20 mg; or

d. pravastatin >40 mg; or

e. lovastatin 40 mg; or

f. fluvastatin XL 80 mg; or

g. fluvastatin 40 mg twice daily; or

h. pitavastatin > 2 mg

for at least the past three months; and

3. The recipient has received add-on therapy with ezetimibe to the maximum tolerable dose of statin for at least the past two weeks or the recipient has a contraindication to ezetimibe therapy; and

4. The LDL-C after therapy for at least the past three months was ≥ 100 mg/dL (HeFH) or ≥ 70 mg/dL (clinical atherosclerotic cardiovascular disease); and

5. Statin therapy will be continued with PCSK-9 therapy.

c. Or the recipient experienced an adverse reaction to at least two statins, the statins and adverse reactions must be documented in the recipient's medical record.

d. Or the recipient has a labeled contraindication to all statins, the contraindication is documented in the recipient's medical record.

2. Recertification Request (The recipient must meet all criteria (a-d))

   a. The recipient has been adherent with PCSK-9 inhibitor therapy; and

   b. The recipient has been adherent with statin therapy or the recipient has a labeled contraindication to statin therapy; and

   c. The recipient is continuing a low-fat diet and exercise regimen; and

   d. The recipient has achieved a reduction in LDL-C level.

3. Prior Authorization Guidelines

   a. Prior authorizaiton approvals will be for:

      1. Initial request: six months

      2. Recertification request: one year

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

INTRODUCTION

- Cardiovascular disease (CVD) is the leading cause of death worldwide and accounts for nearly 1 in 3 deaths in the United States (US). Key cardiovascular (CV) risk factors include smoking, physical inactivity, obesity, hypercholesterolemia, poor nutrition, hypertension, and diabetes mellitus *(American Heart Association [AHA] 2019)*.
- Serum cholesterol is known to be related to atherosclerotic CVD (ASCVD), with low-density lipoprotein cholesterol (LDL-C) being the dominant form of atherogenic cholesterol. LDL-C is a primary cause of atherosclerosis, but other major contributing risk factors include cigarette smoking, hypertension, dysglycemia, and other lipoprotein abnormalities *(Grundy et al 2018).*
- Almost 40% of American adults have total cholesterol serum levels of 200 mg/dL or higher and nearly 1 in 3 have elevated levels of LDL-C (≥ 130 mg/dL) *(AHA 2019)*.
- Familial hypercholesterolemia (FH) is a common and serious genetic condition resulting in severely elevated cholesterol concentrations and increased risk of premature coronary heart disease (CHD) (*Goldberg et al 2011*). Patients can have homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH is estimated to occur in 1 in 200 to 250 adults in the US; HoFH is much rarer with an estimated prevalence of 1:300,000 to 1:400,000, but homozygous patients are more adversely affected by the condition *(Rosenson and Durrington 2019).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that leads to the degradation of hepatocyte LDL-C receptors (LDLR), which results in increased LDL-C levels; by inhibiting PCSK9, LDLR recycling is preserved, and LDL-C levels are subsequently reduced *(Navarese et al 2015*). The PCSK9 inhibitors are administered subcutaneously (SC) every 2 weeks or once monthly.
- Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) *(Grundy et al 2018)*, American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) *(Jellinger et al 2017)*, and the National Lipid Association (NLA) *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy for hypercholesterolemia or CVD, with ezetimibe and the PCSK9 inhibitors being potential adjunctive agents for patients not achieving adequate LDL-C lowering; however, there is no consensus on goal LDL-C levels.
- Medispan class: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Praluent (alirocumab)	-
Repatha (evolocumab)	-

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Praluent (alirocumab)	Repatha (evolocumab)
To reduce the risk of myocardial infarction (MI), stroke, and unstable angina (UA) requiring hospitalization in adults with established CVD	✔	
As an adjunct to diet, alone or in combination with other lipid lowering therapies (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C	✔	✔
As an adjunct to diet and other lipid lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C		✔
To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD		✔

(Prescribing information: Praluent 2019, Repatha 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of alirocumab was evaluated in the ODYSSEY program, which consisted of 10 phase 3, multi-center (MC), double-blind (DB), randomized controlled trials (RCTs) *(Praluent Food and Drug Administration [FDA] Briefing Information).*
  - Patients with HeFH and/or high or very high CV risk were enrolled in 9 of the 10 trials. Eight trials evaluated alirocumab in patients receiving background statin therapy (typically at maximally tolerated doses), whereas 2 trials evaluated alirocumab as monotherapy, including in statin-intolerant patients (ie, ODYSSEY ALTERNATIVE). Ezetimibe was the comparator in the 5 active-controlled (AC) trials, whereas the other 5 trials were placebo-controlled (PC) *(Praluent FDA Briefing Information).*
- The efficacy of evolocumab was evaluated in the PROFICIO program, which consisted of 8 phase 3, MC, DB, RCTs *(Repatha FDA Briefing Information*).
  - In most of the trials, patients with HeFH, HoFH, or primary hyperlipidemia were randomized to receive evolocumab or placebo, and received background statin therapy in both treatment arms, ranging from moderate-intensity statin therapy (eg, atorvastatin 10 mg) to high-intensity statin therapy (eg, atorvastatin 80 mg). In 2 trials, evolocumab was compared to ezetimibe as monotherapy, including in statin-intolerant patients (ie, GAUSS-2 and -3) *(Repatha FDA Briefing Information).*

Familial hypercholesterolemia (FH)

- ODYSSEY FH I-II and HIGH FH compared the efficacy of alirocumab with placebo in patients with HeFH for a 24-week duration. In FH I-II, patients were initiated on alirocumab 75 mg SC every 2 weeks (Q2W) with an up-titration dosing strategy, whereas patients in HIGH FH were initiated on alirocumab 150 mg SC Q2W with no up-titration (*Kastelein et al 2015*).
  - ODYSSEY FH I-II were 2 identical, PC, RCTs evaluating alirocumab in 735 patients with HeFH and LDL-C > 70 mg/dL with a history of CVD or LDL-C > 100 mg/dL without history of CVD. Patients had a mean baseline LDL-C level of 140 mg/dL while receiving statin therapy; 85% of patients received high-intensity statin therapy, and 60% received ezetimibe. After 24 weeks of treatment, alirocumab reduced LDL-C by 58% and 51% in FH I and FH II, respectively, compared to placebo ($p < 0.0001$) *(Kastelein et al 2015*).
  - ODYSSEY HIGH FH evaluated alirocumab in 107 patients with HeFH and LDL-C > 160 mg/dL. Patients had a mean baseline LDL-C of approximately 200 mg/dL while receiving statin therapy; about 70% of patients were receiving high-intensity statins (eg, atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily). Compared to placebo, alirocumab reduced LDL-C by 39% at 24 weeks ($p < 0.0001$) *(Ginsberg et al 2016*).
- ODYSSEY ESCAPE was a DB, PC, RCT that randomized patients with HeFH who were undergoing lipoprotein apheresis to alirocumab 150 mg SC Q2W (n = 41) or placebo (n = 21) for 18 weeks. Patients were treated in combination with their usual apheresis schedule for 6 weeks. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53.7% in alirocumab-treated patients vs 1.6% in placebo-treated patients; subsequently, apheresis was discontinued in 63.4% of alirocumab-treated patients, and the rate was at least halved in 92.7% *(Moriarty et al 2016).*
- In RUTHERFORD-2, patients with HeFH were randomized to receive evolocumab 140 mg SC Q2W (n = 111), evolocumab 420 mg SC every 4 weeks (Q4W) (n = 110), or placebo (n = 110) for 12 weeks. Patients had a mean baseline LDL-C level of 155 mg/dL while receiving statin therapy; 87% of patients were receiving high-intensity statin therapy, and 62% of patients were receiving ezetimibe. Compared to placebo, evolocumab 140 mg SC Q2W lowered LDL-C by 59% and evolocumab 420 mg SC Q4W by 61% at 12 weeks ($p < 0.0001$) *(Raal et al 2015a).*
- The TESLA Part B trial randomized 50 patients with HoFH on stable lipid-lowering therapy (LLT) to evolocumab 420 mg SC Q4W (n = 33) or placebo (n = 17) for 12 weeks. Patients in the evolocumab group had a mean baseline LDL-C of 356 mg/dL; those in the placebo group had a mean baseline LDL-C of 336 mg/dL. Treatment with evolocumab reduced LDL-C by 23.1%, whereas patients treated with placebo had an increase in LDL-C by 7.9% (treatment difference -30.9%; $p < 0.0001$); however, the mean on-treatment LDL-C remained significantly elevated at 271 mg/dL *(Raal et al 2015b).*
- Alirocumab has not been evaluated in patients with HoFH.

Patients with hypercholesterolemia not adequately controlled on other LLTs

- ODYSSEY COMBO I and II were 2 similarly designed 24-week, DB, RCTs in high CVD risk patients who were inadequately controlled with maximally tolerated statin therapy. Patients were included if they had a history of CVD with LDL-C ≥ 70 mg/dL, or LDL-C ≥ 100 mg/dL and CHD risk equivalents. In COMBO I, patients were randomized to alirocumab 75 mg SC Q2W (n = 209) or placebo (n = 107), whereas in COMBO II, patients were randomized to alirocumab 75 mg SC Q2W (n = 479) or ezetimibe 10 mg daily (QD) (n = 241). Both studies employed the up-titration protocol *(Cannon et al 2015, Kereiakes et al 2015).*
  - In COMBO I, 78.2% of patients had a history of CHD, 43.0% had CHD risk equivalents, and 43.0% had type 2 diabetes mellitus (T2DM). All patients but 1 received statin therapy, with 62.7% receiving high-dose statin therapy. From a baseline of 100.3 mg/dL for patients with alirocumab and 104.6 mg/dL for patients with placebo, alirocumab reduced LDL-C by 45.9% compared with placebo ($p < 0.0001$) *(Kereiakes et al 2015).*
  - In COMBO II, 75.6% of patients had CHD, 31.0% had CHD risk equivalents, and 30.7% had T2DM. All patients but 1 received statin therapy, with 66.7% receiving high-dose statin therapy. From a mean baseline of 109.0 mg/dL for patients with alirocumab and 105.0 mg/dL for patients with ezetimibe, alirocumab reduced LDL-C by 29.8% compared with ezetimibe ($p < 0.0001$) *(Cannon et al 2015).*
- ODYSSEY OPTIONS I and II were 24-week, DB, RCTs evaluating alirocumab in combination with atorvastatin or rosuvastatin in patients with hypercholesterolemia who were inadequately controlled (very high CV risk and LDL-C ≥ 70 mg/dL or high CV risk and LDL-C ≥ 100 mg/dL). In ODYSSEY OPTIONS I, 355 patients on atorvastatin 20 or 40 mg at baseline were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, (3) double their atorvastatin dose, or (4) switch to rosuvastatin. In ODYSSEY OPTIONS II, 305 patients on rosuvastatin 10 or 20 mg were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, or (3) double their rosuvastatin dose *(Bays et al 2015, Farnier et al 2016, Robinson et al 2014a).*
  - In OPTIONS I, among patients receiving atorvastatin 20 and 40 mg, greater LDL-C reduction was achieved with add-on alirocumab (44.1%, 54.0%), compared with add-on ezetimibe (20.5%, 22.6%), doubling atorvastatin dose (4.8%, 5.0%), or switching to rosuvastatin (21.4%; $p < 0.001$ for all comparisons) *(Robinson et al 2014a, Bays et al 2015).*
  - In OPTIONS II, in patients receiving rosuvastatin 10 mg, greater LDL-C reduction was achieved with add-on alirocumab (50.3%) compared with add-on ezetimibe (14.4%), or doubling the rosuvastatin dose (16.3%) ($p < 0.0001$ for all comparisons). In the rosuvastatin 20 mg group, the addition of alirocumab reduced LDL-C by 36.3%, but the comparisons with the ezetimibe and double rosuvastatin groups did not reach statistical significance *(Farnier et al 2016).*
- LAPLACE-2 was a phase 3 study evaluating evolocumab in combination with various statin regimens. Patients with different LDL-C levels and different background LLT were first randomized to 1 of 5 open-label (OL) statin regimens (atorvastatin 80 mg, rosuvastatin 40 mg, atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) for 4 weeks, and then randomized to evolocumab 140 mg SC Q2W or 420 mg SC Q4W (n = 1117), ezetimibe 10 mg QD (n = 221; patients receiving atorvastatin only), or placebo (n = 558) for 12 weeks. Compared with placebo, evolocumab further reduced LDL-C by at least 60% in all statin groups; compared with ezetimibe, evolocumab further reduced LDL-C by approximately 40% in patients receiving low-dose and high-dose atorvastatin (*Robinson et al 2014b*).
- Alirocumab was evaluated specifically in patients with diabetes in ODYSSEY DM-INSULIN and ODYSSEY DM-DISLIPIDEMIA *(Leiter et al 2017, Ray et al 2018).*
  - ODYSSEY DM-INSULIN was a 24-week, DB, PC, RCT in patients with type 1 diabetes mellitus (T1DM) (n = 71) or T2DM (n = 441) treated with insulin and not controlled on maximally-tolerated statin therapy. Patients were randomized to receive alirocumab 75 mg SC Q2W with an up-titration strategy or placebo. Alirocumab reduced LDL-C from baseline to week 24 by 49% and 47.8% vs placebo in patients with T2DM and T1DM, respectively (both $p < 0.0001$). Glycated hemoglobin (HbA1c) and fasting blood glucose levels remained stable and treatment-emergent adverse effects (TEAEs) were comparable across the groups *(Leiter et al 2017).*
  - ODYSSEY DM-DISLIPIDEMIA was a 24-week, OL, RCT in patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥ 100 mg/dL and triglycerides ≥ 150 mg/dL but < 500 mg/dL) not adequately controlled despite maximally tolerated statin therapy. Patients were randomized to receive alirocumab (n = 276) or usual care (n = 137). Alirocumab reduced non-HDL-C by 37.3% vs 4.7% with usual care ($p < 0.0001$). No clinically meaningful effect was seen on HbA1c or change in number of glucose-lowering agents. The rate of TEAEs was similar between the groups *(Ray et al 2018).*

Monotherapy and patients unable to tolerate statin therapy

- ODYSSEY MONO was a 24-week, DB, AC, RCT comparing alirocumab monotherapy with ezetimibe in patients with hypercholesterolemia. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 52) with the option to titrate to 150 mg Q2W, or ezetimibe 10 mg QD (n = 51). At 24 weeks, alirocumab reduced LDL-C from baseline by 47.2% vs 15.6% for ezetimibe (treatment difference: -31.6%; p < 0.0001). Adverse effects (AEs) were similar between the groups *(Roth and McKenney 2015).*
- MENDEL-2 was a 12-week, DB, AC, PC, RCT comparing evolocumab monotherapy with ezetimibe or placebo in patients with hypercholesterolemia. Patients were randomized to receive evolocumab 140 mg SC Q2W (n = 153) or 420 mg SC Q4W (n = 153), ezetimibe 10 mg QD (n = 154), or placebo (n = 155). Evolocumab reduced LDL-C from baseline by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all comparisons). TEAEs and muscle-related AEs were comparable across the groups *(Koren et al 2014b).*
- ODYSSEY ALTERNATIVE was a 24-week, DB, AC, RCT comparing alirocumab with ezetimibe and atorvastatin in statin-intolerant patients. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 126) with the option to titrate to 150 mg, ezetimibe 10 mg QD (n = 125), or atorvastatin 20 mg QD (n = 63) (validation arm). Alirocumab reduced LDL-C by 45% from baseline vs 14.6% for ezetimibe (treatment difference -30.4%; p < 0.0001). Alirocumab was better-tolerated than atorvastatin in patients in terms of muscle-related TEAEs (32.5% vs 46.0%; p = 0.042) *(Moriarty et al 2015).*
- GAUSS-2 and -3 both compared evolocumab with ezetimibe in statin-intolerant patients *(Nissen et al 2016, Stroes et al 2014)*.
  - GAUSS-2 was a 12-week, DB, PC, AC trial with patients randomized to evolocumab 140 mg SC Q2W + placebo orally QD (n = 103), evolocumab 420 mg SC Q4W + placebo orally daily (n = 102), or ezetimibe 10 mg orally QD + placebo SC Q2W or Q4W (n = 102). Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences vs ezetimibe of 37% and 39% (p < 0.001). Muscle-related TEAEs occurred in 12% of evolocumab-treated patients vs 23% of ezetimibe-treated patients *(Stroes et al 2014).*
  - GAUSS-3 was a 24-week, 2-stage RCT in patients with a history of intolerance to 2 or more statins (N = 511). Phase A used a 24-week crossover protocol with atorvastatin or placebo to identify patients experiencing muscle-related AEs only to atorvastatin. In Phase B, patients experiencing intolerance only to atorvastatin were randomized to ezetimibe 10 mg QD (n = 73) or evolocumab 420 mg SC Q4W (n = 145) for 24 weeks. From baseline, evolocumab reduced LDL-C by 52.8% vs 16.7% for ezetimibe (treatment difference: -36.1%; p < 0.001). Muscle-related AEs were reported in 20.7% of evolocumab-treated patients and 28.8% of ezetimibe-treated patients *(Nissen et al 2016).*

Longer term efficacy and safety

- ODYSSEY LONG TERM was a 78-week, DB, PC, RCT in which high CVD risk patients who were receiving maximally tolerated statin therapy and had an LDL-C ≥ 70 mg/dL were randomized to receive alirocumab 150 mg SC Q2W (n = 1553) or placebo (n = 788) (*Robinson et al 2015*).
  - Compared with placebo, alirocumab reduced LDL-C by 61.9% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 78 weeks (56.0% vs placebo; p < 0.001).
  - In a post hoc analysis, patients treated with alirocumab had a lower rate of adjudicated composite CVD events (ie, CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization) compared with placebo (1.7% vs 3.3%, respectively; hazard ratio [HR] 0.52; 95% confidence interval [CI], 0.31 to 0.90; p = 0.02). However, there was no difference when including all positively adjudicated CVD events (ie, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization) (4.6% vs 5.1%, respectively; p = 0.68).
  - The frequency of AEs was similar in both groups (81.0% vs 82.5%, respectively), as were discontinuation rates (7.2% vs 5.8%, respectively).
- The OSLER studies enrolled 4465 patients who had completed a phase 2 or phase 3 trial with evolocumab, and randomly assigned them to OL evolocumab plus standard of care (SOC) or SOC alone. OSLER-1 enrolled patients from phase 2 trials to receive evolocumab 420 mg SC Q4W, whereas OSLER-2 enrolled patients from phase 3 trials to receive evolocumab 140 mg SC Q2W or 420 mg SC Q4W depending on patient choice. The parent trials included patients on statin therapy (70.1%), as well as patients who were statin intolerant or were not on other LLTs *(Koren et al 2014a, Sabatine et al 2015).*
  - Compared with SOC alone, evolocumab reduced LDL-C by 58.8% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 48 weeks (58.4% vs SOC; p < 0.001).

- In a prespecified exploratory analysis, patients treated with evolocumab had a lower rate of CVD events (ie, death, MI, UA requiring hospitalization, coronary revascularization, stroke, transient ischemic attack [TIA], heart failure requiring hospitalization) (0.95% vs 2.18% with SOC; HR 0.47; 95% CI, 0.28 to 0.78; p = 0.003).
- The frequency of AEs was similar in both groups (69.2% vs 64.8%, respectively), as were serious AEs (7.5% in each group). Although uncommon overall, neurocognitive AEs were more frequent with evolocumab (0.9% vs 0.3% with SOC).
- In 5-year results from OSLER-1, evolocumab demonstrated sustained mean LDL-C reductions over time, with patients maintaining a 56% reduction from baseline at year 5. Evolocumab was not associated with an increase in AEs or neutralizing antibodies over time *(Koren et al 2018 [abstract])*.

- DESCARTES was a 52-week RCT comparing evolocumab with placebo in 901 hypercholesterolemic patients with a range of CVD risk. Prior to the treatment phase, patients were assigned to 1 of 4 background LLT groups in a 4- to 12-week OL run-in period: diet alone, diet with atorvastatin 10 mg QD, diet with atorvastatin 80 mg QD, or diet with atorvastatin 80 mg QD and ezetimibe 10 mg QD. Patients were intensified to the next level of background LLT if they did not reach their LDL-C goal per current guidelines (Adult Treatment Panel [ATP] III). After the run-in period, patients were then randomized in a 2:1 ratio to evolocumab 420 mg SC Q4W (n = 599) or placebo (n = 302). After 52 weeks, evolocumab reduced LDL-C in all 4 LLT groups compared with placebo (55.7%, 61.6%, 56.8%, 48.5%, respectively; p < 0.001 for all comparisons) *(Blom et al 2014).*

Cardiovascular outcomes

- FOURIER, a DB, PC, RCT, was the first completed CV outcomes trial for the PCSK9 inhibitors. The trial enrolled 27,564 high-risk patients with CVD and LDL-C levels ≥ 70 mg/dL while receiving optimized LLT (99.7% of patients were receiving moderate- or high-intensity statins). Patients were randomized to receive evolocumab (either 140 mg SC Q2W or 420 mg SC Q4W) or placebo, while remaining on their baseline LLT. The primary endpoint was a composite of CV death, MI, stroke, hospitalization for UA, and coronary revascularization *(Sabatine et al 2017)*.
  - At 48 weeks, the least-squares mean (LSM) percentage reduction in LDL-C levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL to 30 mg/dL (p < 0.001).
  - The composite endpoint occurred in 9.8% of evolocumab-treated patients vs 11.3% of placebo-treated patients (treatment difference of 1.5%; HR 0.85; 95% CI, 0.79 to 0.92; p < 0.001) during a median follow-up period of 26 months. The benefit was driven by reduction of MI, stroke, and coronary revascularization; no benefit was identified in CV death or death from any cause.
- ODYSSEY OUTCOMES was a DB, PC, RCT enrolling 18,924 patients who had experienced an acute coronary syndrome (ACS) between 1 to 12 months prior and had inadequate control of their lipids (eg, LDL-C ≥ 70 mg/dL) despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (75 mg or 150 mg SC Q2W) or placebo in addition to their baseline LLT to treat to an LDL-C target of 25 to 50 mg/dL. The primary endpoint was a composite of CHD death, non-fatal MI, ischemic stroke, and UA requiring hospitalization. Median follow-up was 2.8 years *(Schwartz et al 2018).*
  - Compared to placebo, alirocumab reduced the overall risk of the primary composite outcome (alirocumab: 9.5% vs placebo: 11.1%; HR 0.85; 95% CI, 0.78 to 0.93; p = 0.0003) and was associated with a lower risk of non-fatal MI (alirocumab: 6.6% vs placebo: 7.6%; HR 0.86; 95% CI, 0.77 to 0.96; p = 0.006), ischemic stroke (alirocumab: 1.2% vs placebo: 1.6%; HR 0.73; 95% CI, 0.57 to 0.93; p = 0.01), and UA (alirocumab: 0.4% vs placebo: 0.6%; HR 0.61; 95% CI, 0.41 to 0.92; p = 0.02).
    - For the primary composite endpoint, the absolute benefit of alirocumab was greater among patients with a baseline LDL-C level ≥ 100 mg/dL (HR 0.76; 95% CI, 0.65 to 0.87) compared to patients with lower baseline levels; however, the analysis on this subgroup was not prespecified.
  - Alirocumab was associated with a lower risk of all-cause mortality (alirocumab: 3.5% vs placebo: 4.1%; HR 0.85; 95% CI, 0.73 to 0.98; nominal p = 0.026), and there were also numerically fewer CHD deaths (alirocumab: 2.2% vs placebo: 2.3%; HR 0.92; 95% CI, 0.76 to 1.11; p = 0.38).
  - In a prespecified analysis of 8242 patients eligible for ≥ 3 years follow-up, alirocumab reduced death (HR 0.78; 95% CI, 0.65 to 0.94; p = 0.01). A post hoc analysis found that patients with baseline LDL-C ≥ 100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR 0.71; 95% CI, 0.56 to 0.90; *p*interaction = 0.007). Patients who achieved lower LDL-C values at 4 months (down to ~ 30 mg/dL) appeared to be at lower risk of subsequent death. (*Steg et al 2019*).

Meta-analyses

A Cochrane Review meta-analysis of 20 studies (N = 67,237) comparing PCSK9 inhibitors with placebo (13 RCTs), ezetimibe (2 RCTs), or ezetimibe and statins (5 RCTs) was conducted to quantify short-, medium-, and long-term effects of PCSK9 inhibitors on lipid parameters and on the incidence of CVD *(Schmidt et al 2017)*.
  - At 24 weeks, PCSK9 inhibitors decreased LDL-C by 53.86% vs placebo, 30.20% vs ezetimibe, and 39.20% vs ezetimibe and statins.
  - Compared with placebo, PCSK9 inhibitors decreased the risk of CVD events, with a risk difference (RD) of 0.91% (odds ratio [OR] 0.86; 95% CI, 0.80 to 0.92). Compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect on CVD risk, although with considerable uncertainty (RD 1.06%; OR 0.45; 95% CI, 0.27 to 0.75).
  - Compared with placebo, PCSK9 inhibitors probably had little or no effect on mortality (RD 0.03%; OR 1.02; 95% CI, 0.91 to 1.14).
- A meta-analysis was conducted on 35 RCTs comparing treatment with a PCSK9 inhibitor to no PCSK9 inhibitor in adults with hypercholesterolemia (N = 45,539). Compared with no PCSK9 inhibitor use, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in MI (PCSK9 inhibitor: 2.3% vs control: 3.6%; OR 0.72; 95% CI, 0.64 to 0.81), stroke (1.0% vs 1.4%; OR 0.80; 95% CI, 0.67 to 0.96), and coronary revascularization (4.2% vs 5.8%; OR 0.78; 95% CI, 0.71 to 0.86). Use of a PCSK9 inhibitor was not significantly associated with a decrease in all-cause mortality (1.9% vs 2.2%; OR 0.71; 95% CI, 0.47 to 1.09) or CV mortality (1.1% vs 1.3%; OR 1.01; 95% CI, 0.85 to 1.19) *(Karatasakis et al 2017)*.
- In an updated meta-analysis involving 62,281 patients from 28 RCTs, the CV outcomes of PCSK9 inhibitor therapy (N = 33,204) vs placebo (N = 29,077) were assessed (*Casula et al 2019*). Results revealed no significant difference in all-cause mortality between the groups (OR 0.93; 95% CI, 0.85 to 1.03). However, PCSK9 inhibitor therapy was associated with a significant reduction in CV events as compared to placebo (OR 0.83; 95% CI, 0.78 to 0.87). Additionally, the occurrence of stroke and MI were significantly reduced with the PCSK9 inhibitors. CV mortality was not significantly different between the groups (OR 0.94; 95% CI, 0.83 to 1.07)

CLINICAL GUIDELINES

- The updated ACC/AHA (2018) treatment guidelines for hypercholesterolemia emphasize reducing the risk of ASCVD through lipid management. In patients with clinical ASCVD, LDL-C should be reduced with high-intensity or maximally tolerated statin therapy. In very high risk ASCVD, an LDL-C threshold of 70 mg/dL should be utilized to consider the addition of non-statins to maximally tolerated statin therapy. If the addition of ezetimibe does not decrease LDL-C levels < 70 mg/dL, the addition of a PCSK9 inhibitor is reasonable. Similarly, in patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), high-intensity statin therapy should be initiated, but if the LDL-C level remains ≥ 100 mg/dL, adding ezetimibe may be reasonable. If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. The guideline notes that long-term safety (> 3 years) with the PCSK9 inhibitors is uncertain and cost-effectiveness is low at mid-2018 prices *(Grundy et al 2018)*.
- The NLA guideline (2015) recommends that the central focus of pharmacotherapy in hypercholesterolemia be moderate- or high-intensity statin therapy, and acknowledges that RCT evidence is limited in guiding combination drug therapy in patients receiving maximally tolerated statin therapy whose atherogenic cholesterol remains elevated above treatment goals *(Jacobson et al 2015)*.
  - The NLA Expert Panel evidence-based recommendations on treatment with PCSK9 inhibitors are summarized in Table 3. Patients with ASCVD and/or additional risk factors who have not met their LDL-C goals should be considered for adjunct therapy with a PCSK9 inhibitor; it is emphasized that clinicians should reinforce the importance of statin therapy and attention to lifestyle therapy with each patient visit *(Orringer et al 2017)*.

Table 3. 2017 NLA expert panel PCSK9 inhibitor recommendations

Disorder	LDL-C/Non-HDL-C for threshold for Rx (mg/dL)
ASCVD + additional risk factors	≥ 70/ ≥ 100
Progressive ASCVD	≥ 70/ ≥ 100
LDL-C ≥ 190, age 40 to 79 with no uncontrolled risk factors or key additional risk markers	≥ 100/ ≥ 130
LDL-C ≥ 190, age 40 to 79 with uncontrolled risk factors or key additional risk	≥ 70/ ≥ 100

markers	
LDL-C ≥ 190, age 18 to 39 with uncontrolled risk factors or key additional risk markers or FH causing mutation	≥ 100/ ≥ 130
HoFH phenotype	≥ 70/ ≥ 100
ASCVD + statin intolerance	Clinical judgment

- The AACE/ACE guidelines recommend LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. PCSK9 inhibitors should be considered as adjunct therapy in patients with FH or clinical CVD who are unable to reach their LDL-C goals with maximally tolerated statin therapy *(Jellinger et al 2017).*

SAFETY SUMMARY

- Warnings/precautions
  - Hypersensitivity reactions (eg, pruritus, rash, urticaria), including some serious events (eg, hypersensitivity vasculitis, hypersensitivity reactions requiring hospitalization), have been reported with alirocumab and evolocumab treatment.
- Adverse effects
  - Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
- Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, symptoms associated with abetalipoproteinemia, a familial condition with minimal or nonexistent LDL-C levels (eg, fat malabsorption syndromes, hepatic steatosis, progressive neurologic degenerative disease, retinitis pigmentosa, acanthocytosis), were not observed *(McKenney 2015).* Rates of overall AEs, serious AEs, and neurocognitive AEs among patients achieving very low LDL-C levels were similar to those among the overall group *(Robinson et al 2015, Sabatine et al 2015, Sabatine et al 2017).* The long-term effects of very low LDL-C levels by alirocumab or evolocumab are unknown *(Praluent Prescribing Information 2019, Repatha Prescribing Information 2019).*
- Neurocognitive AEs occurred infrequently, but more often in patients treated with alirocumab (1.2% vs 0.5% with placebo) and evolocumab (0.9% vs 0.3% with placebo) in longer-term safety analyses *(Robinson et al 2015, Sabatine et al 2015).*
  - The EBBINGHAUS trial evaluated cognitive function in 1204 patients enrolled in the FOURIER trial and identified no important cognitive differences between patients treated with evolocumab vs placebo over a median follow-up of 19 months *(Giugliano et al 2017).*
  - A meta-analysis of 14 Phase 2 and 3 alirocumab trials found no significant differences in rates of patient-reported neurocognitive TEAEs between alirocumab and controls (placebo or ezetimibe). No association was found between neurocognitive TEAEs and LDL-C < 25 mg/dL *(Harvey et al 2018).*
- There are no data available on use of alirocumab or evolocumab in pregnant or lactating women to inform a drug-associated risk.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Praluent (alirocumab)	Single-dose pre-filled syringe: 75 mg/mL, 150 mg/mL Single-dose pre-filled pen: 75 mg/mL, 150 mg/mL	SC	Starting dose: 75 mg every 2 weeks or 300 mg every 4 weeks If LDL-C response is inadequate, the dosage may be adjusted to the maximum dose of 150 mg every 2	The safety and efficacy of alirocumab have not been established in the pediatric population.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			weeks HeFH patients undergoing LDL apheresis: 150 mg every 2 weeks; can be administered without regard to timing of apheresis	
Repatha (evolocumab)	Single-dose pre-filled syringe: 140 mg/mL Single-dose pre-filled autoinjector: 140 mg/mL Single-dose pre-filled cartridge with on-body infusor: 420 mg/3.5 mL	SC	Established ASCVD or primary hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly HoFH: 420 mg once monthly	The safety and efficacy of evolocumab in combination with diet and other LDL-C lowering therapies in adolescents with HoFH were established based on data from a 12-week, PC trial that included 10 adolescents (ages 13 to 17 years old) with HoFH. Safety and effectiveness have not been established in pediatric patients with HoFH who are younger than 13 years old. Safety and effectiveness have not been established in pediatric patients with primary hyperlipidemia or HeFH.

See the current prescribing information for full details

CONCLUSION

- CVD is the leading cause of death worldwide *(AHA 2019)*. Serum cholesterol is known to be related to ASCVD, with LDL-C being the dominant form of atherogenic cholesterol *(Grundy et al 2018).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit PCSK9, leading to substantial LDL-C reduction *(Navarese et al 2015*). The PCSK9 inhibitors are administered SC every 2 weeks or once monthly.
  - Alirocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C and to reduce the risk of MI, stroke, and UA requiring hospitalization in adults with established CVD.
  - Evolocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; as an adjunct to diet and other LLTs (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C; and to reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD.
- The efficacy and safety of alirocumab and evolocumab have been demonstrated across numerous clinical trials in various patient populations. The PCSK9 inhibitors offer substantial LDL-C lowering and both have been shown to reduce CV events in high-risk patients, although benefit on mortality is still unclear.
- Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
  - Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, rates of overall AEs, serious AEs, and neurocognitive AEs among these patients were similar to those among the overall group. The long-term effects of very low LDL-C levels by alirocumab or evolocumab are still unknown.

- Current guidelines from the ACC/AHA *(Grundy et al 2018)*, AACE/ACE *(Jellinger et al 2017)*, and the NLA *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy, with ezetimibe and the PCSK9 inhibitors as potential second-line agents for patients not achieving adequate LDL-C lowering. Patients with ASCVD or at high risk for ASCVD may benefit from more aggressive LDL-C targets; however, there is no consensus on goal LDL-C levels.

REFERENCES

- American Heart Association. Heart disease and stroke statistics 2019: at-a-glance. AHA Web site. 2019. https://healthmetrics.heart.org/wp-content/uploads/2019/02/At-A-Glance-Heart-Disease-and-Stroke-Statistics-%E2%80%93-2019.pdf. Accessed October 31, 2019.
- Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;jc20151520.
- Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370:1809-1819.
- Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186-1194.
- Casula M, Olmastroni E, Boccalari MT, Tragni E, Pirillo A, Catapano AL. Cardiovascular events with PCSK9 inhibitors: an updated meta-analysis of randomized controlled trials. *Pharmacol Res*. 2019; May;143:143-150. doi: 10.1016/j.phrs.2019.03.021. Epub 2019 Mar 26.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed October 31, 2019.
- Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2016;244:138-146.
- Food and Drug Administration: Controlling cholesterol with statins. https://www.fda.gov/forconsumers/consumerupdates/ucm293330.htm. Updated February 16, 2017.Accessed October 31, 2019.
- Ginsberg HN, Radar DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016;30(5):473-483.
- Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377(7):633-643.
- Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S1-8. doi: 10.1016/j.jacl.2011.04.003.
- Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018; Nov 10. [Epub ahead of print].
- Harvey PD, Sabbagh MN, Harrison JE, et al. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized phase 2 and 3 controlled trials: a meta-analysis of individual patient data. *Eur Heart J.* 2018;39:374-381.
- Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol*. 2015;9(2):129-169.
- Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017;23(Suppl 2):1-87. doi: 10.4158/EP171764.APPGL
- Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc.* 2017;6:e006910.
- Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J.* 2015;36(43):2996-3003.
- Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906-15.e13.
- Koren MJ, Giugliano RP, Raal FJ, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52 week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. *Circulation*. 2014a;129:234-243.
- Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol*. 2014b;63:2531-40.
- Koren MJ, Sabatine MS, Giugliano RP, et al. Final report of the OSLER-1 study: long-term evolocumab for the treatment of hypercholesterolemia. Presented at: American Heart Association Scientific Sessions 2018; November 10-12, 2018; Chicago, IL.
- Leiter LA, Cariou B, Muller-Wieland D, et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: the ODYSSEY DM-INSULIN randomized trial. *Diabetes Obes Metab*. 2017;19(12):1781-1792.
- McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. *J Clin Lipidol.* 2015;9:170-186.
- Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. *Eur Heart J*. 2016;37(48):3588-3595.
- Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015;9(6):758-769. doi: 10.1016/j.jacl.2015.08.006.
- Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;10.7326/M14-2957.
- Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315(15):1580-1590.
- Orringer CE, Jaconson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an expert panel of the National Lipid Association. *J Clin Lipidol*. 2017;11(4):880-890.
- Praluent [package insert], Bridgewater, NJ: Sanofi-Aventis U.S. LLC; April 2019.

- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed October 31, 2019.
- Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015a;385:341-350.
- Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015b;385:331-340.
- Ray KK, Leiter LA, Muller-Wieland D, et al. Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: the ODYSSEY DM-DYSLIPIDEMIA randomized trial. *Diabetes Obes Metab.* 2018;20(6):1479-1489.
- Repatha [package insert], Thousand Oaks, CA: Amgen Inc.; February 2019.
- Robinson JG, Calhoun HM, Bays HE, et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. *Clin Cardiol*. 2014a;37:597-604.
- Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA*. 2014b;311:1870-1882.
- Robinson JG, Farnier M, Krempf M, et al, for the ODYSSEY LONG TERM investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-1499. doi: 10.1056/NEJMoa1501031
- Rosenson RS, Durrington P. Familial hypercholesterolemia in adults: overview. UpToDate Web site. www.uptodate.com. Updated April 15, 2019. Accessed October 31, 2019. .
- Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. *Future Cardiol*. 2015;11:27-37.
- Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
- Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1500-1509.
- Schmidt AF, Pearche LS, Wilkins JT, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;4:CD011748.
- Schwartz GG, Steg PG, Szarek M, ODYSSEY OUTCOMES Committees and Investigators, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med.* 2018;379(22):2097-2107. doi: 10.1056/NEJMoa1801174.
- Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation*. 2019;140(2):103-112.
- Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63:2541-2548.

Publication Date: December 17, 2019

Prior Authorization Guideline

Guideline Name	Valtoco (diazepam)

Valtoco is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy. Valtoco is indicated for patients 6 years of age and older.

1 . Criteria

Product Name: Valtoco	
Guideline Type	Prior Authorization

Approval Criteria

1. Diagnosis of epilepsy.

AND

2. Prescribed for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern.

AND

3. The prescriber provides a reason or special circumstance that precludes the use of diazepam rectal gel

AND

4. The quantity will not exceed 5 episodes per month.

Nevada Medicaid

Valtoco Utilization
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
No Utilization				

BBBB. Anticonvulsants

Therapeutic Class: Anticonvulsants
Last Reviewed by the DUR Board: January 24, 2019

Anticonvulsants are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

Cannabinoid

Epidiolex® (cannabidiol)

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. The recipient has a diagnosis of Lennox-Gastaut syndrome or Dravet Syndrome; and

   b. The recipient is two years of age or older; and

   c. A recent serum transaminase (ALT and AST) and total bilirubin level has been obtained and is within normal limits; and

   d. The drug is prescribed by or in consultation with a neurologist; and

   e. The total dose does not exceed 20 mg/kg/day (10mg/kg twice daily); and

   f. The medication will be used as adjunctive therapy (the recipient has been taking one or more antiepileptic drugs and has chart notes confirming the presence of at least four convulsive seizures per month).

2. Recertification Request

   a. Documentation of a positive clinical response to Epidiolex® therapy; and

   b. Serum transaminase (ALT and AST) and total bilirubin level has been re-checked per package insert.

3. Prior Authorization Guidelines

   a. Initial prior authorization will be for three months.

   b. Recertification approval will be for 12 months.

   c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

4. For anticonvulsant criteria for children and adolescents, refer to Section N, titled Psychotropic Medications for Children and Adolescents.

Prior Authorization Guideline

Guideline Name	Vivitrol (naltrexone extended-release)

1 . Criteria

Product Name: Vivitrol (naltrexone extended-release)	
Approval Length	6 Month
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following :

1.1 Requested drug is being used to prevent relapse to opioid dependence following opioid detoxification

OR

1.2 Requested drug is being used as a treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of therapy

AND

2 - Requested dose is one injection every month

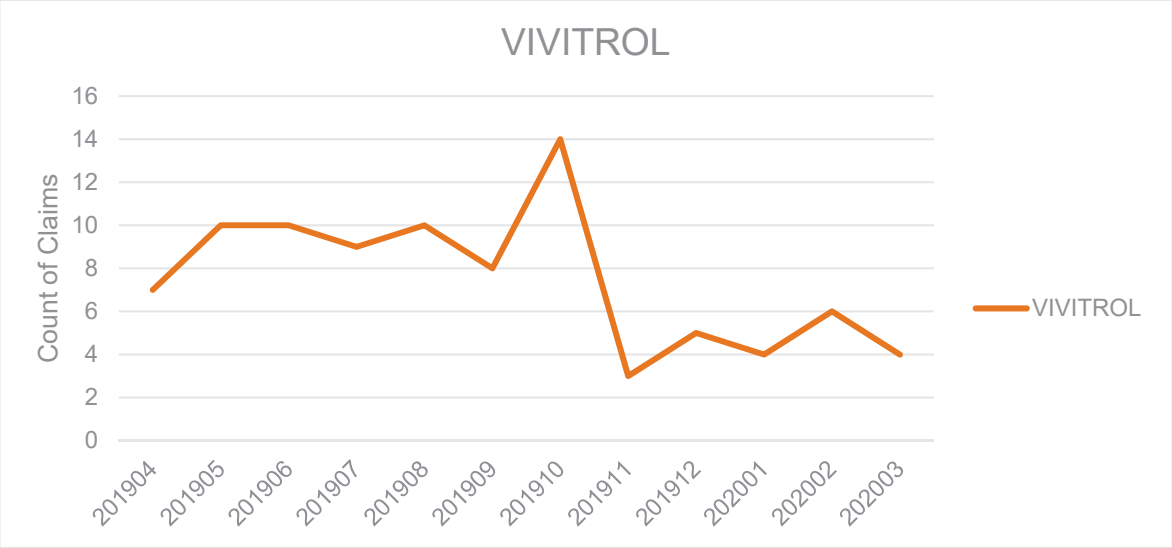
AND

3 - Requested drug will be delivered directly to the requesting prescriber’s office

Nevada Medicaid

Vivitrol Utilization
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Men	Count of Claims	Total Days Supply	Total Quantity
VIVITROL	37	90	2,414	102



BB. Substance Abuse Agents

Therapeutic Class: Narcotic Withdrawal Therapy Agents
Last Reviewed by the DUR Board: April 25, 2019

Buprenorphine/Naloxone and Buprenorphine are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

Buprenorphine/Naloxone

1. Coverage and Limitations

   a. Prior authorization approval will be required for all prescriptions over 24 mg.

   b. Requires diagnosis of opioid dependence.

2. Prior Authorization Guidelines

   a. Prior authorization approval will be for one year.

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Lucemyra™ (lofexidine)

1. Coverage and Limitations

   a. A diagnosis of opioid withdrawal with symptoms due to abrupt opioid discontinuation is required; and

   b. The requested quantity does not exceed 2.88 mg/day for up to 14 days.

2. Prior Authorization Guidelines

   a. Prior authorization approval will be for 14 days.

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Vivitrol® (naltrexone)

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. The drug is being used for an FDA approved indication; and

b. The drug must be delivered directly to the prescriber's office; and

c. The drug is only to be administered once per month; and

d. Routine urine screening and monitoring is recommended.

2. Prior Authorization Guidelines

a. Prior authorization approvals will be for six months.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2020*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act (DATA) of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment [CSAT] 2004*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2020*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) SC injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, and the FDA shows that the product has been discontinued (*Drugs@FDA.gov 2020*).
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents; Agents for Chemical Dependency

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride (HCl)* tablet	✔
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular (IM) injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
buprenorphine/naloxone* sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔
Zubsolv (buprenorphine/naloxone) sublingual tablets	- †

*Brand name product was discontinued; however, generic formulations are available.
†Generic version not anticipated until 2032.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving opioids increased to more than 42,000 deaths in 2016 (*SAMHSA 2018)*.
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths *(SAMHSA 2018, World Health Organization [WHO] 2014)*.
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, most states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2019*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after IM or SC administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2020*).
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio), which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
Evzio (naloxone HCl) auto-injector	-
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	- †

*Brand name product was discontinued; however, generic formulations are available
†Generic product approved by the FDA, but not yet launched

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/ naloxone) film	buprenorphine/ naloxone sublingual tablets	Suboxone (buprenorphine/ naloxone) film	Zubsolv (buprenorphine/ naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder*	✔					

*For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2019, buprenorphine/naloxone sublingual tablets 2019, Bunavail 2019, Sublocade 2019, Suboxone film 2019, Zubsolv 2019*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✔	
Treatment of alcohol dependence	✔	✔
Prevention of relapse to opioid dependence following opioid detoxification		✔

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2019*)

Table 5. FDA-Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔

(*Prescribing information: Lucemyra 2018*)

Table 6. FDA-Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✔		✔
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine		✔	
Diagnosis of suspected or known acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

(*Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid-negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (n = 32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Weiss 2011, Woody et al 2008*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥ 16 mg/day were more likely to continue treatment compared to patients receiving doses < 16 mg/day; however, no significant difference was seen in the percentage of opioid-positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (n = 758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual

tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).

- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019*, *Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2015, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* In a 2019 meta-analysis (N = 150,235 patients across 32 cohort studies), overall mortality rates were higher with methadone vs buprenorphine; however, when comparing time in-treatment to time out-of-treatment, methadone significantly reduced mortality vs buprenorphine (*Bahji et al 2019*). In another meta-analysis that same year (N = 370,611 patients across 30 studies), buprenorphine demonstrated lower all-cause mortality post-medication assisted therapy (MAT) vs methadone or naltrexone. However, all-cause mortality during MAT was lowest with naltrexone, followed by buprenorphine and methadone (*Ma et al 2019*).
- When low doses of buprenorphine were studied (≤ 8 mg/day), high doses of methadone (≥ 50 mg/day) proved to be more efficacious *(Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In another 2019 meta-analysis (N = 847 overdose events across 4 studies), there was no statistically significant difference for retention in treatment between patients who received buprenorphine/naloxone vs buprenorphine or methadone alone (*Dalton et al 2019*).
- In a 24-week, Phase 3, double-blind, placebo-controlled, randomized controlled trial (n = 504), the efficacy and safety of multiple SC injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior to placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with negative self-reports for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Haight et al 2019)*.
- Extended-release IM naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (n = 570). More induction failures were seen with extended-release IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A 12-week, randomized, open-label, noninferiority trial (n = 159) similarly found that extended-release IM naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). A small, randomized, open-label study (n = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (*Sullivan et al 2019*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (n = 264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar results were found in another placebo-controlled trial *(Fishman et al 2019)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Evzio 2016, Narcan 2017*).

- The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).

- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio, 8.58; 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescribing naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).
- A retrospective cohort study including 3,085 patients found that of out-of-hospital naloxone administration improved outcomes for approximately 73% of patients with presumed opioid overdose (*Ashburn et al 2020*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, ASAM, CSAT/U.S., SAMHSA, and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications *(Kampman 2015 [update pending Spring 2020], VHA 2015).*
  - Use of tapered doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the WHO and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*Kampman 2015 [update pending Spring 2020], WHO 2014*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
  - Buprenorphine products have several warnings and precautions, including abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions.

- Concomitant use of buprenorphine with benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).
- The buprenorphine SC injection also has several unique warnings and precautions, including serious harm or death if administered IV (boxed warning); risks associated with treatment of emergent acute pain; and use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2020*).

- Lofexidine has several warnings and precautions, including risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
  - Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
  - The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
  - The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
  - Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
  - Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
  - Monitor patients on naltrexone for the development of depression or suicidality.
  - Warnings unique to extended-release IM naltrexone include injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
  - The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
  - There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
  - Extended-release IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2020*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal (including adverse cardiovascular events).
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment
naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	SC injection	SC	Monthly (minimum 26 days between doses)	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.
Vivitrol (naltrexone extended-release)	IM injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv;	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	generics equivalent to Suboxone tablet)		4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction: titrate in buprenorphine 2 mg to 4 mg increments at approximately 2-hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2-hour intervals)	

See the current prescribing information for full details

Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
-	16 mg/4 mg	11.4 mg/2.9 mg

*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	• After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression. • Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	• The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* • An initial dose may be administered IV. It may be repeated at 2 to 3-minute intervals if the desired degree of counteraction and improvement in	• IM or SC administration may be necessary if the IV route is not available. • The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			respiratory functions are not obtained. *Children:* • The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	intoxication since absorption may be erratic or delayed.
Narcan (naloxone HCl)	Nasal spray	Intranasal	• A single spray should be administered into 1 nostril. • Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) SC injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for moderate-to-severe opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2020*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019, Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.

- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release IM naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release IM naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], VHA 2015).*
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine *(Kampman 2015 [update pending Spring 2020], VHA 2015).*

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approvals of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who

are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015 [update pending Spring 2020]*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.
- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

REFERENCES

- Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend*. 2017;174:58-64.
- Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict*. 2004;13 Suppl 1:S42-66.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Ed. Arlington, VA: American Psychiatric Association; 2013:541-546.
- American Society of Addiction Medicine. Opioid Addiction 2016 Facts & Figures. http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf. Accessed February 7, 2020.
- Ashburn NP, Ryder CW, Angi RM, et al. One-year mortality and associated factors in patients receiving out-of-hospital naloxone for presumed opioid overdose. *Ann Emerg Med*. 2020 Jan 23. pii: S0196-0644(19)31422-2. doi: 10.1016/j.annemergmed.2019.11.022. [Epub ahead of print].
- Bahji A, Cheng B, Gray S, Stuart H. Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. *Acta Psychiatr Scand;* 2019:140(4):313–339. doi: 10.1111/acps.13088
- Bickel WK, Amass L, Crean JP, et al. Buprenorphine dosing every one, two or three days in opioid-dependent patients. *Psychopharmacology (Berl).* 1999;146(2):111-118.
- Bunavail prescribing information. Biodelivery Sciences International, Inc. Raleigh, NC. October 2019.
- Buprenorphine and naloxone tablet prescribing information. Actavis Pharma, Inc. Parsippany, NJ. October 2019.
- Buprenorphine prescribing information. Sun Pharmaceutical Industries, Inc. Cranbury, NJ. May 2019.
- Center for Substance Abuse Treatment; Substance Abuse and Mental Health Services Administration (SAMHSA). Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville (MD): Substance Abuse and Mental Health Services Administration 2004. Available from: http://www.ncbi.nlm.nih.gov/books/NBK64245/. Accessed February 7, 2020.
- Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2012;61(6):101-105.
- Coffin P. Prevention of lethal opioid overdose in the community. UpToDate Web site. http://www.uptodate.com. Updated June 12, 2019. Accessed February 7, 2020.
- Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med.* 2016;165(4):245-252.
- Committee on Substance Use and Prevention (CSUP). Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. *Pediatrics*. 2016 Sep;138(3). http://pediatrics.aappublications.org/content/138/3/e20161893.long. Accessed February 7, 2020.
- Dalton K, Butt N. Does the addition of naloxone in buprenorphine/naloxone affect retention in treatment in opioid replacement therapy?: a systematic review and meta-analysis. *J Addict Nurs*. 2019;30(4):254-260. doi: 10.1097/JAN.0000000000000308.
- Daulouède JP, Caer Y, Galland P, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. *J Subst Abuse Treat*. 2010;38(1):83-89.
- Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. *BMC Public Health*. 2014;14:297.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 7, 2020.
- Evzio FDA Summary Review. Drugs@FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2017/208411s001SumR.pdf. Accessed February 7, 2020.
- Evzio prescribing information. Kaleo, Inc. Richmond, VA. October 2016.
- Fareed A, Vayalapalli S, Casarella J, et al. Effect of buprenorphine dose on treatment outcome. *J Addict Dis*. 2012;31(1):8-18.
- Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend*. 2002;65:283-290.
- FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. FDA website. Updated September 26, 2017. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications. Accessed February 7, 2020.
- FDA: Joint Meeting of Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee. Sublocade FDA Briefing Document. October 31, 2017. https://www.fda.gov/media/108382/download. Accessed February 7, 2020.

- Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary-care based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(12):1947-1954.
- Fishman M, Tirado C, Alam D, et al. Safety and efficacy of lofexidine for medically managed opioid withdrawal: a randomized controlled clinical trial. J Addict Med. 2019;13(3):169-176. doi: 10.1097/ADM.0000000000000474.
- Fry A. Alvogen and Reddy's cleared over US rivals to suboxone. Updated July 15, 2019. Available from: https://generics.pharmaintelligence.informa.com/GB140502/Alvogen-and-Reddys-Cleared-Over-US-Rivals-To-Suboxone?vid=Pharma. Accessed February 7, 2020.
- Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349(10):949-958.
- Gibson A, Degemhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long term mortality. *Addiction.* 2008; 103(3):462-468.
- Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol*. 2015;2(1):10.
- Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. *Drug Alcohol Depend*. 2017;176:79-88. doi: 10.1016/j.drugalcdep.2017.02.020.
- Gowing L, Farrell M, Ali R, White JM. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2016;(5):CD002024. doi: 10.1002/14651858.CD002024.pub5.
- Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2017;2:CD002025. doi: 10.1002/14651858.CD002025.pub5.
- Gunderson EW, Hjelmström P, Sumner M; 006 Study Investigators. Effects of a higher-bioavailability buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone film for the treatment of opioid dependence during induction and stabilization: a multicenter, randomized trial. *Clin Ther*. 2015;37(10):2244-2255.
- Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2019;393(10173):778-790. doi: 10.1016/S0140-6736(18)32259-1.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267:2750–2755.
- Kakko J, Svanborg KD, Kreek MJ, et al. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet*. 2003;361(9358):662-668.
- Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl*. 2008;10:5-18.
- Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med*. 2015;9(5):358-367.
- Kelly AM, Derr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *MJA*. 2005; 182:24-27.
- Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction.* 2009;104:2067-2074.
- Kleber HD, Weiss RD, Anton RF, et al. for the American Psychiatric Association Workgroup on Substance Use Disorders, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry*. 2006;163(8 Suppl):5-82.
- Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. *J Addict Med*. 2011;5(4):254-263.
- Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. *J Psychopharmacol*. 2017;31(8):1046-1055. doi: 10.1177/0269881117711710.
- Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet.* 2018;391(10118):309-318. doi: 10.1016/S0140-6736(17)32812-X.
- Lexicomp Online. Lexicomp Web site. 2020. http://online.lexi.com/lco/action/home. Accessed February 7, 2020.
- Ling W, Wesson D, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401-407.
- Lintzeris N, Leung SY, Dunlop AJ, et al. A randomized controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend*. 2013;131:119-126.
- Lucemyra prescribing information. US WorldMeds, LLC. Louisville, KY. May 2018.
- Ma J, Bao Y, Wang R, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry*. 2019;24(12):1868-1883. doi: 10.1038/s41380-018-0094-5
- Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014;2:CD002207.
- Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend*. 2010;108(1-2):110-114.
- Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *Am J Emerg Med*. 2010;28(3):296-303.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2020. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed February 7, 2020.
- Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011;(4):CD001333. doi: 10.1002/14651858.CD001333.pub4.
- Naloxone prescribing information. West-Ward Pharmaceuticals. Eatontown, NJ. March 2015.
- Naltrexone tablet prescribing information. SpecGx LLC. Webster Groves, MO. July 2017.

- Narcan Nasal Spray FDA Summary Review. Drugs@FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf. November 18, 2015. Accessed February 7, 2020.
- Narcan nasal spray prescribing information. Adapt Pharma, Inc. Radnor, PA. September 2019.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 7, 2020.
- Perry AE, Neilson M, Martyn-St James M, et al. Pharmacological interventions for drug-using offenders. *Cochrane Database Syst Rev.* 2015;6: CD010862. doi: 10.1002/14651858.CD010862.pub2.
- Petitjean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend.* 2001;62:97-104.
- Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther*. 1999;66(3):306-314.
- REMS@FDA [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available at: http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed February 7, 2020.
- Robertson TM, Hendey GW, Stroh G, et al. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care.* 2009;13(4):512-515.
- Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, et al. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. *Arch Med Sci.* 2014;10(2):309-314.
- SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 18-4742. Substance Abuse and Mental Health Services Administration Web site. 2018. https://store.samhsa.gov/system/files/sma18-4742.pdf. Accessed February 7, 2020.
- SAMHSA. Treatment Improvement Protocol (TIP) 63: Medications for opioid use disorder. June 2019. Available at: https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf. Accessed February 7, 2020.
- Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713-720.
- Schottenfeld RS, Pakes J, O'Connor P, et al. Thrice-weekly vs daily buprenorphine maintenance. *Biol Psychiatry*. 2000;47(12):1072-1079.
- Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol*. 2008;11:641-653.
- Strain E. Pharmacotherapy for opioid use disorder. UpToDate Web site. https://www.uptodate.com. Updated January 28, 2020. Accessed February 7, 2020.
- Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther.* 2011;89(3):443-449.
- Sublocade prescribing information. Indivior, Inc. North Chesterfield, VA. October 2019.
- Suboxone film prescribing information. Indivior, Inc. North Chesterfield, VA. October 2019.
- Sullivan MA, Bisaga A, Pavlicova M, et al. A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. *Am J Psychiatry*. 2019;176(2):129-137. doi: 10.1176/appi.ajp.2018.17070732.
- Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry*. 2017;74(12):1197-1205. doi: 10.1001/jamapsychiatry.2017.3206.
- US Department of Health & Human Services (HHS). Naloxone: the opioid reversal drug that saves lives. December 2018. Available at: https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf. Accessed February 7, 2020.
- Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2015. Available at: http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp . Accessed February 7, 2020.
- Vivitrol prescribing information. Alkermes, Inc. Waltham, MA. September 2019.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-1246.
- Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008;300(17):2003-2011.
- World Health Organization: Community management of opioid overdose. WHO Web site. 2014. http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/. Accessed February 7, 2020.
- Zubsolv prescribing information. Orexo US, Inc. New York, NY. October 2019.

Publication Date: March 17, 2020

Prior Authorization Guideline

Guideline Name	Somavert (pegvisomant)

1 . Indications

Drug Name: Somavert (pegvisomant)
Acromegaly Indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum insulin-like growth factor-I (IGF-I) levels.

2 . Criteria

Product Name: Somavert	
Approval Length	12 Week(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of acromegaly

AND

2 - One of the following: [2]

2.1 Inadequate response to one of the following:

- Surgery

- Radiation therapy
- Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

OR

2.2 Not a candidate for all of the following:

- Surgery
- Radiation therapy
- Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

AND

3 - Trial and failure, contraindication, or intolerance to generic octreotide (a somatostatin analogue) [2]

AND

4 - Prescribed by or in consultation with an endocrinologist

Product Name: Somavert	
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Somavert therapy (such as biochemical control; decrease or normalization of IGF-1 levels)

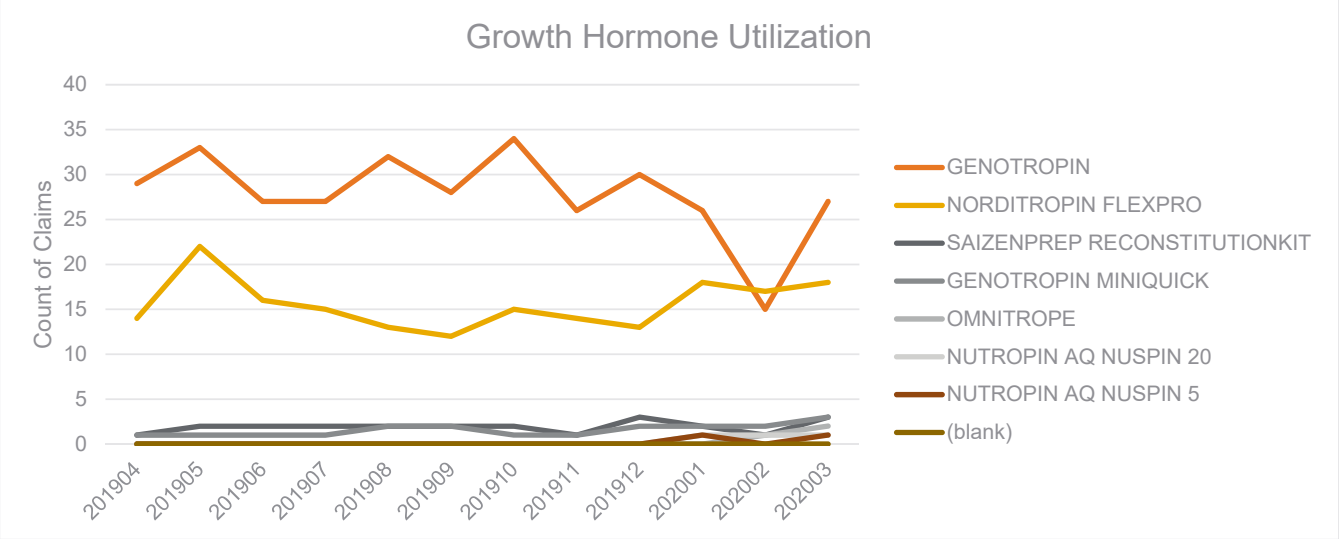
3 . References

1. Somavert Prescribing Information. Pfizer Inc. New York, NY. September 2019.
2. Katznelson L, Laws ER, Melmed S, et al. Acromegaly: An endocrine society clinical practice guideline, J Clin Endocrinol Metab, 2014 Nov;99(11):3933-51. doi: 10.1210/jc.2014-2700. Epub 2014 Oct 30.

Nevada Medicaid

Growth Hormone Utilization
Fee for Service
April 1, 2019 - March 31, 2020

Drug Name	Count of Men	Count of Claims	Total Days Supply	Total Quantity
NORDITROPIN FLEXPRO	33	187	5,253	854
GENOTROPIN	42	334	9,435	1,531
NUTROPIN AQ NUSPIN 5	1	2	176	32
SAIZENPREP RECONSTITUTIONKIT	2	23	666	111
OMNITROPE	1	3	90	14
GENOTROPIN MINIQUICK	4	19	644	644
NUTROPIN AQ NUSPIN 20	1	3	84	12



D. Growth Hormones

Therapeutic Class: Growth Hormone
Last Reviewed by the DUR Board: July 25, 2019

Growth Hormones are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

a. Approval will be given if the following criteria are met and documented:

1. Children (with open epiphyses and with remaining growth potential) must meet all of the following:

a. The recipient has had an evaluation by a pediatric endocrinologist or pediatric nephrologist with a recommendation for growth hormone therapy; and

b. The recipient has had an evaluation ruling out all other causes for short stature; and

c. The recipient is receiving adequate replacement therapy for any other pituitary hormone deficiencies, such as thyroid, glucocorticoids or gonadotropic hormones.

The recipient must then meet one of the following:

1. The recipient has a diagnosis of Noonan Syndrome, Prader-Willi Syndrome or Turner Syndrome and their height is at least two standard deviations below the mean or below the fifth percentile for the patient's age and gender and the bone age is less than 16 years for male recipients or less than 14 years for female recipients; or

2. The recipient has a diagnosis of Prader-Willi Syndrome; or

3. The recipient has a diagnosis of Turner Syndrome, is female and has a bone age of less than 14 years; or

4. The recipient has a diagnosis of chronic renal insufficiency (<75 mL/minute), and their height is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender; or

5. The recipient has a diagnosis of being small for gestational age, the recipient is two years of age or older, and the height

is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender; or

6. The recipient is a newborn infant with evidence of hypoglycemia, and has low growth hormone level (<20 ng/mL), low for age insulin like growth factor (IGF)-1 or IGF binding protein (BP) 3 (no stimulation test required for infants); or

7. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation), and their height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender and their bone age is less than 16 years for male or less than 14 years for female.

   And recipient must meet one of the following:

   a. The recipient has failed two growth hormone stimulation tests (<10 ng/mL); or

   b. The recipient has failed one growth hormone stimulation test (<10 ng/mL) and one IGF-1 or IGFBP-3 test; or

   c. The recipient has failed one growth hormone stimulation test (<10 ng/mL) or IGF-1 or IGFBP-3 test and they have deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH) or antidiuretic hormone (ADH)).

2. Adults (with closed epiphyses, and no remaining growth potential) must meet all of the following:

   a. The recipient is being evaluated by an endocrinologist; and

   b. The recipient is receiving adequate replacement therapy for any other pituitary hormone deficiencies, such as thyroid, glucocorticoids or gonadotropic hormones; and

   c. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation); and

The recipient must then meet one of the following:

1. The recipient has failed two growth hormone stimulation tests (<5 ng/mL); or

2. The recipient has failed one growth hormone stimulation test (<5 ng/mL) and one IGF-1 or IGFBP-3 test; or

3. The recipient has failed one growth hormone stimulation test (<5 ng/mL) or IGFBP-3 test and has deficiencies in three or more pituitary axes (i.e., TSH, LH, FSH, ACTH, ADH), and has severe clinical manifestations of growth hormone deficiency as evident by alterations in body composition (e.g., decreased lean body mass, increased body fat), cardiovascular function (e.g., reduced cardiac output, lipid abnormalities) or bone mineral density.

3. Continued authorization will be given for recipients (up to age 21, with remaining growth potential) who meet all of the following:

   a. The recipient has a diagnosis of chronic renal insufficiency, growth hormone deficiency, hypothalamic pituitary disease, newborn infant with evidence of hypoglycemia, Noonan Syndrome, Prader-Willi Syndrome, small for gestational age or Turner Syndrome; and

   b. The recipient's epiphyses are open; and

   c. The recipient's growth rate on treatment is at least 2.5 cm/year; and

   d. The recipient does not have evidence of an expanding lesion or tumor formation; and

   e. The recipient has not undergone a renal transplant.

4. Continued authorization will be given for recipients (age 21 years and older, with closed epiphyses and no remaining growth potential) who meet all of the following:

   a. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease; and

   b. There is documentation of improvement in clinical manifestations associated with growth hormone deficiency.

b. Serostim® (somatropin)

Recipients must meet all of the following:

1. The recipient has a diagnosis of Human Immune Deficiency Virus (HIV) with wasting or cachexia; and

2. The medication is indicated to increase lean body mass, body weight and physical endurance; and

3. The recipient is receiving and is compliant with antiretroviral therapy; and

4. The recipient has experienced an involuntary weight loss of >10% pre-illness baseline or they have a body mass index of <20 kg/m^2; and

5. The recipient has experienced an adverse event, allergy or inadequate response to megestrol acetate, or the recipient has a contraindication to treatment with this agent; and

6. The recipient has experienced an adverse event, allergy or inadequate response to an anabolic steroid (e.g., testosterone, oxandrolone, nandrolone) or the recipient has a contraindication to treatment with these agents.

c. Zorbtive® (somatropin)

Recipients must meet all of the following:

1. The recipient has a diagnosis of short bowel syndrome; and

2. The recipient is age 18 years or older; and

3. The medication is being prescribed by or following a consultation with a gastroenterologist; and

4. The recipient is receiving specialized nutritional support (e.g., high carbohydrate, low-fat diets via enteral or parenteral nutrition).

2. Prior Authorization Guidelines

a. Prior authorization approval will be 12 weeks for Serostim® (somatropin).

b. Prior authorization approval will be six months for initial authorization (for all somatropin products except for Serostim®).

c. Prior authorization approval will be one year for continuing treatment (for all somatropin products except Serostim®).

d. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Growth Hormone

INTRODUCTION

- Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases, and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Another physiological effect of GH is stimulation of cartilage growth (*Molitch et al 2011*).
- Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A patient's growth patterns are compared to the established norms. The clinical manifestations of GHD vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients present with early severe growth failure, delayed bone age, central disposition of body fat and very low serum concentrations of GH, insulin-like growth factor-1 (IGF-1) and IGF binding protein-3. These patients are also more prone to hypoglycemia, prolonged jaundice, microphallus in males and giant cell hepatitis. GHD in pediatric patients with partial deficiency may be more difficult to diagnose, as these manifestations may not be as obvious (*Molitch et al 2011*).
- Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated and continued until cessation of linear growth. Therapy should be initiated as soon as possible, as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age (*Molitch et al 2011*).
- Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous (SC) injection, are currently the most widely utilized. Due to the variability in individual response to therapy, after initial dosing, the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. A patient's growth velocity, as compared to a similar population, should also be monitored to determine if the growth response is adequate (*Molitch et al 2011*).
- Possible explanations for an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH, or concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (eg, decreased to less than 2.5 centimeters per year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood (*Molitch et al 2011*).
- The majority of pediatric patients with idiopathic, isolated GHD in their childhood have normal GH secretion during late adolescence and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies, and/or those with structural defects in the hypothalamic-pituitary region rarely recover the ability to secrete GH as an adult. Therefore, retesting may not be required (*Molitch et al 2011*).
- GHD may also occur in adult patients. Approximately 15% to 20% of adult-onset GHD represents the continuation of childhood-onset GHD into maturity; the remainder is adult-onset acquired from damage to the pituitary gland or hypothalamus. GHD is associated with increased metabolic syndrome, increased cardiovascular morbidity and mortality rates, reduced lean body mass, increased abdominal adiposity, early atherosclerosis, dyslipidemia, coagulation abnormalities, insulin resistance, decreased bone mineral density, and a decreased quality of life (*Reed et al 2013*). The role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults is not as well established and includes improvement in bone mineral density, sense of well-being, muscle strength, and lipid profile. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood- or adult-onset (*Molitch et al 2011*).
- All of the GH preparations contain somatropin, otherwise known as recombinant human GH. The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease (CKD), Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene, Noonan syndrome, and idiopathic short stature.
- The majority of preparations are also indicated for the treatment of GHD in adults. Of note, Serostim is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults, while Zorbtive is approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support. Specific FDA-

approved indications for the various GH preparations are outlined in Table 2. All of the available GH preparations are available for SC injection, and there are currently no generics available within the class.
- GH preparations are available in various formulations, and several delivery devices are available. The dosing device may be a factor in patient adherence with the prescribed regimen.
- Medispan Class: Growth Hormones

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Genotropin (somatropin)	-
Humatrope (somatropin)	-
Norditropin Flexpro (somatropin)	-
Nutropin AQ (somatropin)	-
Omnitrope (somatropin)	-
Saizen (somatropin)	-
Sersotim (somatropin)	-
Zomacton (somatropin)	-
Zorbtive (somatropin)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Genotropin	Humatrope	Norditropin Flexpro	Nutropin AQ	Omnitrope	Saizen	Serostim	Zomacton	Zorbtive
Growth failure associated with chronic renal insufficiency before renal transplant				✔					
Growth failure associated with Noonan syndrome			✔						
Growth failure associated with Prader-Willi syndrome	✔		✔		✔				
Growth failure associated with short-stature homeobox-containing gene deficiency		✔						✔	
Growth failure associated with Turner syndrome	✔	✔	✔	✔	✔			✔	
Growth failure in children born small for gestational age	✔	✔	✔		✔			✔	
Growth hormone deficiency	✔	✔	✔	✔	✔	✔		✔	
Idiopathic short stature	✔	✔	✔	✔	✔			✔	
Human immunodeficiency virus-associated wasting or cachexia							✔		
Treatment of short bowel syndrome in patients receiving nutritional support									✔

(Prescribing information: *Genotropin 2019, Humatrope 2019, Norditropin Flexpro 2018, Nutropin AQ 2016, Omnitrope 2019, Saizen 2018, Serostim 2019, Zomacton 2018, Zorbtive 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are limited head-to-head clinical trials comparing different GH preparations to one another.

- Clinical data support the use of GH for the treatment of growth failure associated with chronic renal insufficiency. A meta-analysis of 16 RCTs (N = 809) evaluating the effects of GH in children with CKD found that patients who were treated with GH had a greater increase in mean height velocity (3.88 cm) than those who received either no treatment or placebo after 1 year (*Hodson et al 2012*). A retrospective, matched control cohort study found that long-term therapy with GH (mean 4.2 years) reduced linear growth deceleration in children with CKD and improved final height (*Bizzarri et al 2018*).
- Clinical trials have demonstrated efficacy of GH for the treatment of growth failure in patients with Noonan syndrome. A randomized controlled trial evaluating GH in patients with Noonan syndrome found a positive effect of GH on linear growth. Specifically, there was a significantly greater change in height standard deviation score, and bone maturation was accelerated with GH compared to no treatment. In this trial, data also suggest that once treatment with GH is discontinued, “catch-down” (artificially stimulated growth declines once GH is discontinued) growth can occur (*Noordam et al 2001*). In a follow-up analysis of 29 patients treated with GH for a median of 6.4 years, a total of 22 children reached an adult height in the normal range (*Noordam et al 2008*). In a study of 65 patients enrolled in the National Cooperative Growth Study (NCGS) database, it was found that treatment with GH led to gains over predicted height of 9.2 cm in females and 10.9 cm in males (*Romano et al 2009*).
- Clinical trials have demonstrated the significant benefits of GH in pediatric patients with Prader-Willi syndrome in accelerating growth and in improving body composition. Benefits were also observed in improving bone mineral density, lipid profiles, energy expenditure, strength and agility, and pulmonary function (*Carrel et al 1999, Carrel et al 2004, Festen et al 2008, Lindgren et al 1997, Lindgren et al 1998, Lindgren et al 1999, Myers et al 1999, Myers et al, 2007*). Data from 1 trial suggested that growth velocity declines dramatically once treatment is discontinued (*Lindgren et al 1997*).
- Humatrope demonstrated efficacy in increasing first-year height velocity in patients with Short Stature Homeobox-containing gene deficiency when compared to no treatment ($p < 0.0001$) (*Blum et al 2007*).
- Several clinical trials have demonstrated that GH significantly increases the growth rate of pediatric patients with Turner syndrome. Overall, various dose ranging trials did not consistently demonstrate a superior weight-based GH dosing regimen over another; all doses of GH were beneficial. In addition, data suggested that increases in height are greatest during the first year of therapy (*Baxter et al 2007, Bertrand et al 1996, Massa et al 1995, Nienhuis et al 1993, Sas et al 1999a, Takano et al 1989a, Takano et al 1989b, Takano et al 1989c, Takano et al 1993, Takano 1995, van Pareren et al 2003, van Teunenbroek et al 1996*). A Cochrane Review of 4 randomized controlled trials demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short-term growth in patients with Turner syndrome by approximately 3 cm during the first year of treatment. Despite the increase, the final height achieved was still below the normal range (*Baxter et al 2007*).
- For the treatment of growth failure in pediatric patients born small for gestational age, clinical trials have demonstrated the significant benefits of GH on increasing growth rates (*Arends et al 2003, Bannink et al 2010, Boguszewski et al 1998, Bozzola et al 2004, Chatelain et al 1994, De Schepper et al 2008, de Zegher et al 1996, de Zegher et al 2005, Jung et al 2009, Maiorana et al 2009, Sas et al 1999b*). Data from individual clinical trials and 3 meta-analyses found that response to GH therapy is dose-dependent, and higher doses of GH resulted in additional gain (*de Zegher et al 1996, de Zegher et al 2005*).
- Treatment with GH has been shown to increase height velocity in both prepubertal and pubertal pediatric patients with GHD (*Coelho et al 2008, Cohen et al 2002, de Muinck Keizer-Schrama et al 1992, Kriström et al 2009, MacGillivray et al 1996, Mauras et al 2000, Romer et al 2009, Sas et al 2010, Shih et al 1994, Wilson et al 1985*). Two head-to-head trials demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared 3 GH preparations (Genotropin, Humatrope, and Saizen), while the second evaluated 2 preparations (Genotropin and Omnitrope) (*Romer et al 2009, Shih et al 1994*).
- In pediatric patients with idiopathic short stature, somatropin has been shown to increase first-year growth velocity and final height (*Albertsson-Wikland et al 2008, Bryant et al 2007, Deodati et al 2011, Finkelstein et al 2002, Hopwood et al 1993, Kriström et al 2009, van Gool et al 2010, Wit et al 2005*). Additionally, once daily compared to 3 times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity (*Bryant et al 2007, Finkelstein et al 2002*).
- A registry study evaluated the long-term effectiveness and safety of GH in South Korean pediatric patients ≥ 2 years of age with GHD, idiopathic short stature, Turner syndrome, small for gestational age, and chronic renal failure. Interim analysis of 5-year data for 2024 patients (7324 patient-years) found that most patients showed beneficial effect on height standard deviation score for up to 4 years, with the most prominent effect observed within 1 year of treatment initiation. The incidence of adverse events was low, and most cases of neoplasm were benign and/or unrelated to GH therapy (*Rhie et al 2019*).

- A systematic review and meta-analysis of 54 placebo-controlled, randomized controlled trials enrolling over 3400 patients found that GH therapy was associated with reduced body fat and increased lean mass in adults with GHD (*Hazem et al 2012*). Eleven of 16 trials that assessed quality of life outcomes reported positive outcomes, but a meta-analysis was not possible. Furthermore, results from meta-analyses and randomized controlled trials have demonstrated that treatment with GH was associated with improved cardiac function and bone mineral density (*Barake et al 2014, Davidson et al 2004, Maison et al 2003*). However, there are currently conflicting data with regard to the effect of GH on cognitive function, quality of life, and exercise capacity (*Arwert et al 2005, Falleti et al 2006, Rubeck et al 2009, Widdowson, 2010*).
- In patients with human immunodeficiency virus-associated wasting, Serostim has been shown to increase body weight, lean body mass, and work output. However, effects on quality of life were variable (*Moyle et al 2004, Schambelan et al 1996*).
- A meta-analysis assessed the safety and efficacy of GH with or without glutamine supplementation for adult patients with short bowel syndrome; 5 studies were included in the review. Human GH with or without glutamine appeared to provide benefit in terms of increased weight (median [MD] 1.66 kg; 95% confidence interval [CI], 0.69 to 2.63; p = 0.0008), lean body mass (MD 1.93 kg; 95% CI, 0.97 to 2.9; p = 0.0001), energy absorption (MD 4.42 Kcal; 95% CI, 0.26 to 8.58; p = 0.04) and nitrogen absorption (MD 44.85 g; 95% CI, 0.2 to 9.49; p = 0.04) for patients with short bowel syndrome. One randomized controlled trial which focused on parenteral nutrition (PN) requirements demonstrated decreased PN volume, calories, and number of infusions in patients who received GH with or without glutamine supplementation. Only patients who received GH with glutamine maintained statistically significant PN reductions at 3-month follow-up. The results suggested a positive effect of GH on weight gain and energy absorption. However, after cessation of therapy, the effects returned to baseline in the majority of the trials (*Wales et al 2010*).

CLINICAL GUIDELINES

- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, GHD in childhood cancer survivors, Noonan syndrome, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2017, National Kidney Foundation 2009, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need, and the likelihood of adherence.
- Treatment guidelines recommend offering GH therapy to adult patients with proven GHD and no contraindications (*Fleseriu et al 2016*). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (*Fleseriu et al 2016, Yuen et al 2019).* The 2019 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, which focus on adults and patients transitioning from pediatric to adult care, state that no evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- Small studies evaluating the use of GH in short bowel syndrome have yielded conflicting results; methodological differences limit definitive conclusions on the efficacy of GH. In carefully selected patients who are candidates for growth factor treatment, the glucagon-like peptide-2 analog, teduglutide, is recommended as first-line therapy (*Pironi et al 2016*).

SAFETY SUMMARY

- Contraindications to GH products include active malignancy, diabetic retinopathy, hypersensitivity to the agent or any of its excipients, acute critical illness, and use for growth promotion in children with closed epiphyses. Somatropin is also contraindicated in children with Prader-Willi syndrome who are severely obese, have severe respiratory impairment, or have a history of upper airway obstruction or sleep apnea (Genotropin, Humatrope, Norditropin Flexpro, Nutropin AQ, Omnitrope, Saizen, Zomacton).
- Key Warnings/Precautions:
  - Somatropin may contribute to the increased mortality in patients with acute critical illness due to complications from open heart surgery, abdominal surgery, accidental trauma, or respiratory failure.
  - Somatropin may increase progression or recurrence of intracranial neoplasms, particularly meningiomas in patients treated with radiation to the head for their first neoplasm.

- The Safety and Appropriateness of GH treatments in Europe (SAGhE) study, which followed almost 24,000 patients for an average of 14.8 years per patient, found that GH therapy does not increase the risk for leukemia or other cancers in patients with isolated growth failure as compared with the age-matched general population. GH was associated with a modest increase in risk for a secondary cancer in patients with a primary cancer diagnosis. In patients with other non-cancer primary diagnoses, there was a modest increase in cancer risk, primarily bone or bladder cancer (*Swerdlow et al 2017*).

- Undiagnosed or untreated hypothyroidism may impair optimal response to somatropin.
- Somatropin may decrease insulin sensitivity, and previously undiagnosed diabetes mellitus may be unmasked during treatment.
- Intracranial hypertension and pancreatitis have been reported with somatropin treatment.
- Slipped capital femoral epiphyses and scoliosis can occur in pediatric patients.
- Fluid retention has been associated with somatropin in adult patients.
- Increases in serum levels of inorganic phosphorous, alkaline phosphatase, parathyroid hormone and IGF-1 may occur.
- Tissue atrophy may occur when somatropin is SC administered at the same site over a long period of time.
- Somatropin may reduce serum cortisol levels or unmask central hypoadrenalism in patients at risk for pituitary hormone deficiency.

- Adverse Drug Events: Arthralgia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.
- Drug Interactions: Estrogens, glucocorticoids, and insulin or other hypoglycemic agents.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Genotropin (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Humatrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Norditropin Flexpro (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Nutropin AQ (somatropin)	Injection	SC	Weekly dose divided into 3 to 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Omnitrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Saizen (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Sersotim (somatropin)	Injection	SC	Daily	Injections should be rotated to avoid local irritation.
Zomacton (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Zorbtive (somatropin)	Injection	SC	Daily	Injections should be rotated to help prevent lipoatrophy. Dosage titration is recommended for fluid retention and arthralgia/carpal tunnel syndrome.

See the current prescribing information for full details.

CONCLUSION

- The safety and efficacy of GH therapy in pediatric patients with growth failure are well established. Treatment guidelines recommend the use of somatropin as a treatment option for children with growth failure associated with any of the following: GHD, GHD in childhood cancer survivors, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Clayton et al 2007*, *Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2017, National Kidney Foundation 2009, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need, and the likelihood of adherence.
- For adult patients, guidelines recommend offering GH therapy to those with proven GHD and no contraindications. (*Fleseriu et al 2016).* No evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- There are several GH preparations currently available, which all contain somatropin (recombinant human GH). The various preparations are equally biopotent and have the same natural sequence structure (*Rogol et al 2019*). Differences between products such as device features, dose increments, requirement for reconstitution, and requirement for refrigeration may influence individual patient preferences. All of the available GH preparations are available for SC injection, and there are currently no generics available within the class.
- Common adverse reactions that may be observed with GH therapy include arthralgia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.

REFERENCES

- Albertsson-Wikland K, Aronson AS, Gustafsson J, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. *J Clin Endocrinol Metab*. 2008;93(11):4342-4350.
- Arends NJT, Boonstra VH, Mulder PGH, et al. GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: three-year results of a randomized, controlled GH trial. *Clin Endocrinol (Oxf)*. 2003;59(3):779-787.
- Bannink E, Djurhuus CB, Christensen T, et al. Adult height and health-related quality of life after growth hormone therapy in small for gestational age subjects. *J Med Econ*. 2010;13(2):221-227.
- Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99:852-860.
- Baxter L, Byrant L, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with Turner syndrome. *Cochrane Database Syst Rev*. 2007;(1):CD003887.
- Bertrand AM, Chaussain JL, Job B, et al. Three years of GH treatment in Turner 's syndrome: complex effect of GH dosage on growth parameters. *Clin Endocrinol (Oxf)*. 1996;44(6):665-671.
- Bizzarri C, Lonero A, Delvecchio M, et al. Growth hormone treatment improves final height and nutritional status of children with chronic kidney disease and growth deceleration. *J Endocrinol Invest*. 2018;41(3):325-331.
- Blum WF, Crowe BJ, Quigley CA, et al; SHOX Study Group. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: Two-year results of a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab*. 2007;92(1):219-228.
- Boguszewski M, Albertsson-Wikland K, Aronsson S, et al. Growth hormone treatment of short children born small-for-gestational-age: the Nordic Multicentre Trial. *Acta Paediatr*. 1998;87(3):257-263.
- Bozzola E, Lauriola S, Messina MF, et al. Effect of different growth hormone dosages on the growth velocity in children born small for gestational age. *Horm Res*. 2004;61(2):98-102.
- Bryant J, Baxter L, Cave CB, Milne R. Recombinant growth hormone for idiopathic short stature in children and adolescents. *Cochrane Database Syst Rev*. 2007;(3):CD004440.
- Carrel AL, Moerchen V, Myers SE, et al. Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr*. 2004;145:744-749.
- Carrel AL, Myers SE, Whitman BY, et al. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr*. 1999;132(2):215-221.
- Chatelain P, Job JC, Blanchard J, et al. Dose-dependent catch-up growth after two years of growth hormone treatment in intrauterine growth-retarded children. Belgian and French Pediatric Clinics and Sanofi-Choay (France). *J Clin Endocrinol Metab*. 1994;78(6):1454-1460.
- Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab*. 2007;92(3):804-810.
- Coelho R, Brook CG, Preece MA, et al. A randomized study of two doses of biosynthetic human growth hormone on final height of pubertal children with growth hormone deficiency. *Horm Res*. 2008;70(2):85-88.
- Cohen P, Bright GM, Rogol AD, et al; American Norditropin Clinical Trials Group. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. *J Clin Endocrinol Metab*. 2002;87(1):90-98.
- Cohen P, Rogol AD, Deal CL, et al; 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008;93(11):4210-4217.

- Cook DM, Yuen KC, Biller BM, et al; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients - 2009 update. *Endocr Pract*. 2009;15(Suppl 2):1-29.
- de Muinck Keizer-Schrama SM, Rikken B, Wynne HJ, et al. Dose-response study of biosynthetic human growth hormone (GH) in GH-deficient children: effects on auxological and biochemical parameters. Dutch Growth Hormone Working Group. *J Clin Endocrinol Metab*. 1992;74(4):898-905.
- De Schepper J, Thomas M, Beckers D, et al. Growth hormone treatment and fat redistribution in children born small for gestational age. *J Pediatr.* 2008;152:327-330.
- de Zegher F, Albertsson-Wikland K, Wilton P, et al. Growth hormone treatment of short children born small for gestational age: metanalysis of four independent, randomized, controlled, multicentre studies. *Acta Paediatr Suppl*. 1996;417:27-31.
- de Zegher F, Hokken-Koelega A. Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. *Pediatrics*. 2005;115(4):e458-462.
- Deal CL, Tony M, Hyobye C, et al. Growth Hormone Research Society Workshop Summary: Consensus guidelines for recombinant human growth hormone therapy in Prader-Willi Syndrome. *J Clin Endocrinol Metab*. 2013;98:E1072-E1087.
- Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. *BMJ*. 2011;342:c7157.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed February 20, 2020.
- Festen DAM, de Lind van Wijngaarden R, van Eekelen M, et al. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. *Clin Endocrinol (Oxf).* 2008;69(3):443-451.
- Finkelstein BS, Imperiale TF, Speroff T, et al. Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. *Arch Pediatr Adolesc Med*. 2002;156(3):230-240.
- Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888-3921.
- Genotropin [package insert]. New York, NY: Pharmacia & Upjohn Co.; April 2019.
- Gravholt CH, Andersen NH, Conway GS, et al; International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177(3):G1-G70.
- Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Pediatr*. 2016;86:361-397.
- Hazem A, Elamin MB, Bancos I, et al. Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. *Eur J Endocrinol*. 2012;166(1):13-20.
- Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. *J Pediatr*. 1993;123(2):215-222.
- Humatrope [package insert]. Indianapolis, IN: Eli Lily and Company; October 2019.
- Jung H, Land C, Nicolay C, et al. Growth response to an individualized vs fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. *Eur J Endocrinol*. 2009;160(2):149-56.
- Ketteler M, Block GA, Evenepoel P, et al. Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder: synopsis of the Kidney Disease: Improving Global Outcomes 2017 clinical practice guideline update. *Ann Intern Med*. 2018 Feb 20. doi: 10.7326/M17-2640.
- Kriström B, Aronson AS, Dahlgren J, et al. Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature. *J Clin Endocrinol Metab*. 2009;94(2):483-490.
- Lindgren AC, Hagenas L, Muller J, et al. Effects of growth hormone treatment on growth and body composition in prader-willi syndrome: a preliminary report. The Swedish National Growth Hormone Advisory Group. *Acta Paediatr Suppl*. 1997;423:60-62.
- Lindgren AC, Hagenas L, Muller J, et al. Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favorably. *Acta Paediatr*. 1998;87:28-31.
- Lindgren AC, Ritzen EM; Swedish National Growth Hormone Advisory Group. Five years of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr Suppl.* 1999;433:109-111.
- MacGillivray MH, Baptista J, Johanson A. Outcome of a four-year randomized study of daily vs three times weekly somatropin treatment in prepubertal naive growth hormone-deficient children. Genentech Study Group. *J Clin Endocrinol Metab*. 1996;81(5):1806-1809.
- Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. *Pediatrics*. 2009;124(3):e519-31.
- Massa G, Otten BJ, de Muinck Keizer-Schrama SMPF, et al. Treatment with two growth hormone regimens in girls with Turner syndrome: final height results. *Horm Res*.1995;43:144-146.
- Mauras N, Attie KM, Reiter EO, et al. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. *J Clin Endocrinol Metab*. 2000;85(10):3653-3660.
- Molitch ME, Clemmons DR, Malozowski S; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(6):1587-1609.
- Moyle GJ, Daar ES, Gertner JM, et al; Serono 9037 Study Team. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2004;35(4):367-375.
- Myers SE, Carrel AL, Whitman BY, et al. Physical effects of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr.* 1999 (Suppl);433:112-114.
- Myers SE, Whitman BY, Carrel AL, et al. Two years of growth hormone therapy in young children with Prader-Willi syndrome. *Am J Med Genet A*. 2007;143(5):443-448.
- National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. *Am J Kidney Dis*. 2009;53(3 Suppl 2):S11-104.
- Nienhuis HE, Rongen-Westerlaken C, Wit JM, et al. Results of long-term therapy with growth hormone in two dose regimens in Turner Syndrome. *Horm Res*. 1993;39(Suppl 2):31-36.
- Noordam C, Peer PG, Francois I, De Schepper J, van den Burgt I, Otten BJ. Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11. *Eur J Endocrinol. 2008*;159(3):203-208.

- Noordam C, van der Burgt I, Sengers RCA, et al. Growth hormone treatment in children with Noonan's syndrome: four year results of a partly controlled trial. *Acta Paediatr*. 2001;90:889-894.
- Norditropin Flexpro [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; February 2018.
- Nutropin AQ [package insert]. South San Francisco, CA: Genentech, Inc.; December 2016.
- Omnitrope [package insert]. Princeton, NJ: Sandoz Inc.; October 2019.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 20, 2020.
- Pironi L, Arends J, Bozzetti F, et al; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr*. 2016;35(2):247-307.
- Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency – benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol* (Lausanne). 2013;4(64):1-14. doi: 10.3389/fendo.2013.00064
- Rhie YJ, Yoo JH, Choi JH, et al. Long-term safety and effectiveness of growth hormone therapy in Korean children with growth disorders: 5-year results of LG Growth Study. *PLoS One*. 2019;14(5):e0216927. doi: 10.1371/journal.pone.0216927.
- Rogol AD, Richmond EJ. Treatment of growth hormone deficiency in children. UpToDate Web site. www.uptodate.com. Updated October 30, 2019. Accessed February 20, 2020.
- Romano AA, Dana K, Bakker B, et al. Growth response, near-adult height, and patterns of growth and puberty in patients with Noonan syndrome treated with growth hormone. *J Clin Endocrinol Metab*. 2009;94(7):2338-2344.
- Romer T, Saenger P, Peter F, et al. Seven years of safety and efficacy of the recombinant human growth hormone Omnitrope in the treatment of growth hormone deficient children: results of a phase III study. *Horm Res*. 2009;72(6):359-369.
- Saizen [package insert]. Rockland, MA: EMD Serono Inc.; May 2018.
- Sas T, de Waal W, Mulder P, et al. Growth hormone treatment in children with short stature born small for gestational age: five-year results of a randomized, double-blind, dose-response trial. *J Clin Endocrinol Metab*. 1999[b];84(9):3064-3070.
- Sas TC, de Ridder MA, Wit JM, et al. Adult height in children with growth hormone deficiency: a randomized, controlled, growth hormone dose-response trial. *Horm Res Paediatr*. 2010;74(3):172-181.
- Sas TCJ, De Muinck Keizer-Schrama SMPF, Jansen M, et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. *J Clin Endocrinol Metab*. 1999[a];84(12):4607-4612.
- Schambelan M, Mulligan K, Grunfeld C, et al; Serostim Study Group. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. *Ann Intern Med*. 1996;125(11):873-882.
- Serostim [package insert]. Rockland MA: EMD Serono Inc.; June 2019.
- Shih KC, Ho LT, Kuo HF, et al. Linear growth response to recombinant human growth hormone in children with growth hormone deficiency. *Zhonghua Yi Xue Za Zhi (Taipei)*. 1994;54(1):7-13.
- Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103:2761-2784. doi: 10.1210/jc.2018-01175.
- Swerdlow AJ, Cooke R, Beckers D, et al. Cancer risks in patients treated with growth hormone in childhood: The SAGhE European Cohort Study. J *Clin Endocrinol Metab*. 2017;102(5):1661-1672.
- Takano K, Shizume K, Hibi I, et al. Growth hormone treatment in Turner syndrome: results of a multicentre study in Japan. Committee for the Treatment of Turner's Syndrome. *Horm Res*. 1993;39(Suppl 2):37-41.
- Takano K, Shizume K, Hibi I, et al. Long-term effects of growth hormone treatment on height in Turner syndrome: results of a 6-year multicentre study in Japan. Committee for the Treatment of Turner's Syndrome, *Horm Res.* 1995;43:141-143.
- Takano K, Shizume K, Hibi I. Treatment of 80 patients with Turner's syndrome with recombinant human growth hormone (YM-17798) for one year: the results of a multicentric study in Japan. Committee for the Treatment of Turner's Syndrome. *Endocrinol Jpn*. 1989[b];36(2):253-60.
- Takano K, Shizume K, Hibi I. Treatment of 94 patients with Turner's syndrome with recombinant human growth hormone (SM-9500) for two years--the results of a multicentric study in Japan. Committee for the Treatment of Turner's Syndrome. *Endocrinol Jpn*. 1989[c];36(4):569-78.
- Takano K, Shizume K, Hibi I. Turner's syndrome: treatment of 203 patients with recombinant human growth hormone for one year. A multicentre study. *Acta Endocrinol (Copenh).* 1989[a];120(5):559-568.
- van Gool SA, Kamp GA, Odink RJ, et al. High-dose GH treatment limited to the prepubertal period in young children with idiopathic short stature does not increase adult height. *Eur J Endocrinol*. 2010;162(4):653-660.
- van Pareren YK, de Muinck Keizer-Schrama SMPF, Stijnen T, et al. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab*. 2003;88(3):1119-1125.
- van Teunenbroek A, De Muinck Keizer-Schrama SMPF, Stijnen T, et al. Yearly stepwise increments of the growth hormone dose results in a better growth response after four years in girls with Turner Syndrome. *J Clin Endocrinol Metab*. 1996;81(11):4013-4021.
- Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. *Cochrane Database Syst Rev*. 2010;(6):CD006321.
- Wilson DM, Baker B, Hintz RL, Rosenfeld RG. Subcutaneous vs intramuscular growth hormone therapy: growth and acute somatomedin response. Pediatrics. 1985;76(3):361-364.
- Wit JM, Rekers-Mombarg LT, Cutler GB, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *J Pediatr*. 2005;146(1):45-53.
- Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. *Endocr Pract*. 2019;25(11):1191-1232.
- Zomacton [package insert]. Parsippany, NJ: Ferring Pharmaceuticals, Inc.; July 2018.
- Zorbtive [package insert]. Rockland, MA: EMD Serono, Inc.; September 2019.

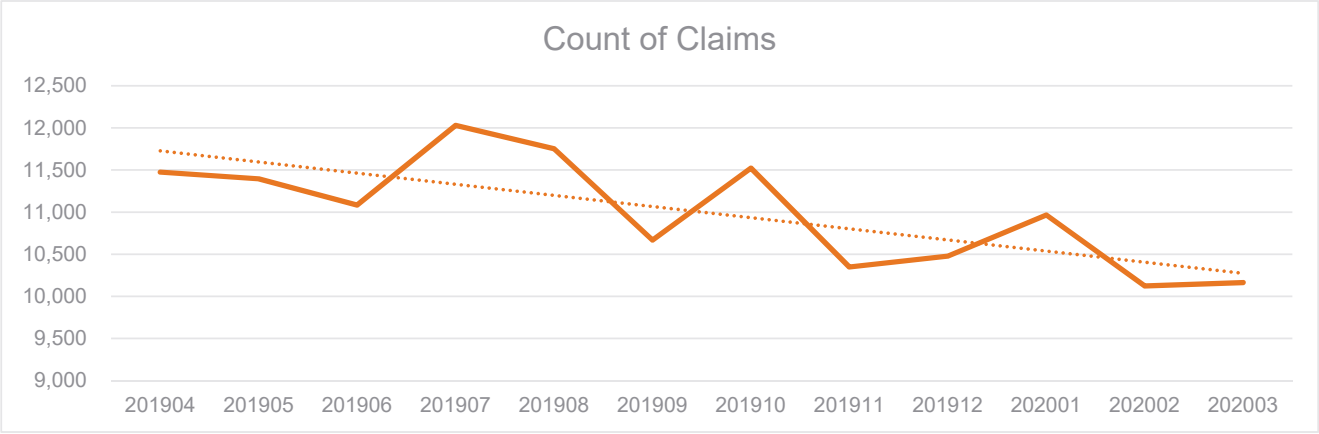
Publication Date:

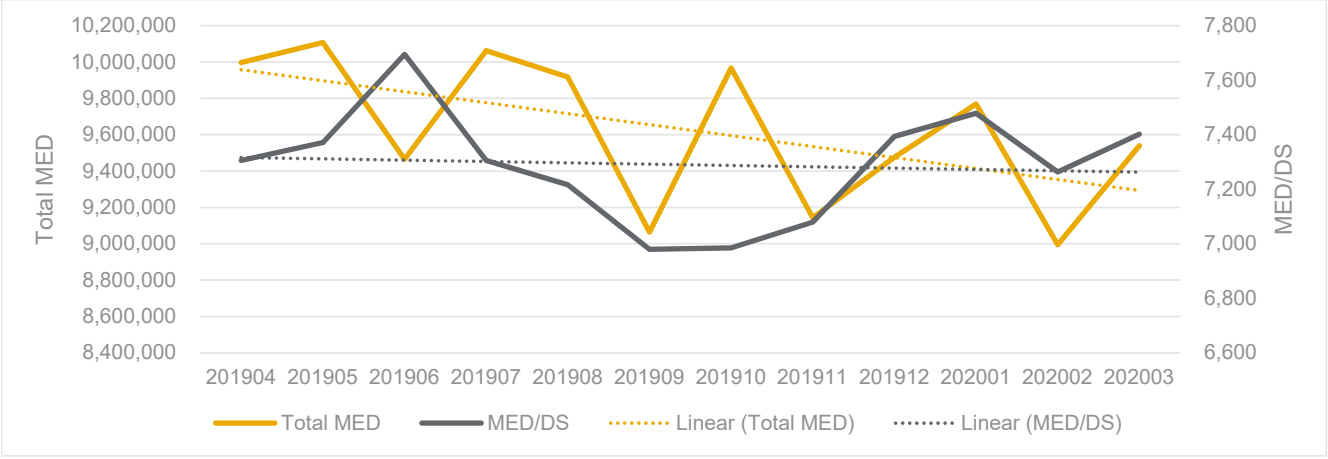
Board Requested Reports

Nevada Medicaid

Opioid Utilization Summary
Fee for Service
April 1, 2019 - March 31, 2020

Date Filled	Count of Men	Count of Claims	Total Days Supply	Total Quantity	Total MED	MED/DS
201904	8,118	11,475	209,425	697,331	9,996,919	7,306
201905	7,999	11,394	211,330	711,129	10,106,744	7,371
201906	7,921	11,083	198,752	656,214	9,464,760	7,694
201907	8,253	12,029	212,377	699,904	10,061,659	7,305
201908	8,143	11,753	211,904	693,734	9,917,509	7,216
201909	7,786	10,666	195,954	638,162	9,064,267	6,979
201910	8,186	11,522	213,416	702,797	9,966,408	6,985
201911	7,645	10,347	194,784	644,369	9,142,883	7,079
201912	7,676	10,476	199,737	663,302	9,475,197	7,393
202001	7,926	10,965	209,121	694,110	9,768,819	7,479
202002	7,607	10,123	193,158	636,042	8,994,588	7,263
202003	7,478	10,163	207,550	685,145	9,539,301	7,402





Opioid Utilization by Prescriber - Top 10

Fee for Service Medicaid

Quarter 4, 2019 and Quarter 1, 2020

2020 Q1 By MED

Prescriber	Specialty	City	Cnt of Members	Cnt of Claims	Days Supply	Total Qty	Total MED	MED/DS	MED/Member/DS
A	MD - Anesthesiolgist	Reno	164	404	11,644	48,067	643,691	1,554	881
B	PA - Orthopedic	Las Vegas	201	404	11,675	38,286	570,341	2,075	1,482
C	MD - Pain Spec	Las Vegas	153	365	10,162	32,984	566,903	1,303	772
D	MD - Anesthesiolgist	Sparks	93	230	6,769	19,320	496,876	2,784	1,988
E	PA	Las Vegas	87	227	6,370	21,131	468,064	1,018	634
F	NP - Pain Spec	Las Vegas	115	242	7,169	21,696	458,874	761	413
G	PA	Las Vegas	131	301	8,781	29,857	392,942	694	263
H	PA - Pain Spec	Las Vegas	81	205	6,135	22,240	389,168	846	350
I	PA	Las Vegas	94	170	4,542	15,396	387,643	1,557	1,002
J	PA	Henderson	35	80	2,315	9,010	381,900	563	327

2020 Q1 By MED/Mem/DS

Prescriber	Specialty	City	Cnt of Members	Cnt of Claims	Days Supply	Total Qty	Total MED	MED/DS	MED/Member/DS
D	MD - Anesthesiolgist	Sparks	93	230	6,769	19,320	496,876	2,784	1,988
B	PA - Orthopedic	Las Vegas	201	404	11,675	38,286	570,341	2,075	1,482
O	MD - Pain Spec	Carson City	50	135	3,938	13,805	226,400	1,796	1,458
K	MD - Rehab	Las Vegas	16	45	1,310	4,015	130,693	1,450	1,357
U	MD - Pain Spec	Las Vegas	11	26	756	4,260	133,200	1,476	1,248
M	NP	Las Vegas	8	14	260	1,448	46,125	1,166	1,166
Q	NP	Las Vegas	95	167	4,755	14,804	377,219	1,653	1,106
S	PA	Pahrump	34	61	1,738	4,616	112,201	1,323	1,096
R	MD - Pain Spec	Henderson	91	115	3,377	10,245	153,932	1,390	1,095
I	PA	Las Vegas	94	170	4,542	15,396	387,643	1,557	1,002

2019 Q4 By MED

Prescriber	Specialty	City	Cnt of Members	Cnt of Claims	Days Supply	Total Qty	Total MED	MED/DS	MED/Member/DS
A	MD - Anesthesiolgist	Reno	177	451	12,951	52,401	670,628	1,388	680
C	MD - Pain Spec	Las Vegas	172	412	11,167	36,506	664,400	1,415	909
P	MD - Pain Spec	Las Vegas	283	435	12,433	37,789	488,052	1,248	702
I	PA	Las Vegas	100	181	4,956	16,692	461,140	1,596	956
F	NP - Pain Spec	Las Vegas	126	260	7,735	22,779	451,493	791	436
Q	NP	Las Vegas	115	219	5,366	17,149	419,620	1,812	1,196
B	PA - Orthopedic	Las Vegas	174	332	9,591	30,403	388,183	1,528	945
G	PA	Las Vegas	118	303	8,998	29,957	386,323	676	254
H	PA - Pain Spec	Las Vegas	84	218	6,036	21,434	377,550	901	425
E	PA	Las Vegas	61	136	4,000	13,615	319,350	894	528

2019 Q4 By MED/Mem/DS

Prescriber	Specialty	City	Cnt of Members	Cnt of Claims	Days Supply	Total Qty	Total MED	MED/DS	MED/Member/DS
K	MD - Rehab	Las Vegas	18	42	1,260	3,915	135,990	1,779	1,679
D	MD - Anesthesiolgist	Sparks	77	154	4,367	12,142	294,373	2,207	1,563
L	PA	Las Vegas	90	134	3,779	12,190	198,865	1,819	1,388
T	PA	Las Vegas	48	63	1,867	6,185	131,515	1,577	1,214
Q	NP	Las Vegas	115	219	5,366	17,149	419,620	1,812	1,196
M	NP	Las Vegas	10	16	397	1,429	82,005	1,432	1,191
U	MD - Pain Spec	Las Vegas	10	27	767	4,764	151,830	1,441	1,169
N	MD - Anesthesiolgist	Las Vegas	11	12	337	1,064	35,470	1,119	1,089
I	PA	Las Vegas	100	181	4,956	16,692	461,140	1,596	956
B	PA - Orthopedic	Las Vegas	174	332	9,591	30,403	388,183	1,528	945

Opioid Utilization by Member - Top 10

Fee for Service Medicaid

Quarter 1, 2020

Member ID Encrypted	Count of Claims	Days Supply	Total Quantity	MED Total	MED/DS
77771952964	3	74	74	53,280	720
22222296971	4	120	520	43,200	360
33330458115	3	90	360	36,000	400
11110100737	3	84	360	36,000	429
22223317921	3	90	180	36,000	400
49044066667	4	91	728	32,760	360
88889910609	3	90	720	32,400	360
82292022223	3	90	720	32,400	360
94483233334	3	90	270	32,400	360
33335396100	4	120	720	32,400	270
22221281059	3	90	720	32,400	360
44446597311	3	90	45	32,400	360
40006322223	3	90	45	32,400	360

Member ID Encrypted	Generic Drug Name	MED Value per Unit	Count of Claims	Total Days Supply	Total Quantity	Total MED
11110100737	MORPHINE SULF TAB CR 100 MG	100	3	84	360	36,000
11110100737	OXYCODONE HCL TAB 10 MG	15	3	84	360	5,400
11110100737	METHADONE HCL TAB 10 MG		3	84	750	
22221281059	OXYCODONE HCL TAB 30 MG	45	3	90	720	32,400
22221281059	METHADONE HCL TAB 10 MG		2	60	240	
22222296971	FENTANYL TD PAT 72H 75MCG/HR	540	2	60	40	21,600
22222296971	OXYCODONE HCL TAB 30 MG	45	2	60	480	21,600
22223317921	MORPHINE SULF TAB CR 200 MG	200	3	90	180	36,000
22223317921	MORPHINE SULF TAB 15 MG	15	3	90	180	2,700
33330458115	OXYCODONE HCL TAB 20 MG	30	2	60	480	14,400
33330458115	MORPHINE SULF TAB CR 100 MG	100	3	90	360	36,000
33335396100	METHADONE HCL TAB 10 MG		4	120	360	
33335396100	OXYCODONE HCL TAB 30 MG	45	4	120	720	32,400
40006322223	FENTANYL TD PAT 72H 100MCG/HR	720	3	90	45	32,400
40006322223	OXYCODONE HCL TAB 30 MG	45	3	90	360	16,200
44446597311	FENTANYL TD PAT 72H 100MCG/HR	720	3	90	45	32,400
44446597311	OXYCODONE HCL TAB 30 MG	45	3	90	540	24,300
49044066667	MORPHINE SULF TAB CR 60 MG	60	4	91	273	16,380
49044066667	OXYCODONE HCL TAB 30 MG	45	4	91	728	32,760
77771952964	FENTANYL TD PAT 72H 100MCG/HR	720	3	74	74	53,280
77771952964	METHADONE HCL TAB 10 MG		3	74	370	
77771952964	OXYCODONE HCL TAB 30 MG	45	3	90	540	24,300
82292022223	OXYCODONE HCL TAB 30 MG	45	3	90	720	32,400
88889910609	OXYCODONE HCL TAB 30 MG	45	3	90	720	32,400
94483233334	OXYCOD TAB ER12H DETER 80MG	120	3	90	270	32,400
94483233334	OXYCODONE W/ APAP TAB 10-325MG	15	3	90	360	5,400

Standard DUR Reports

Nevada Medicaid

Top 10 Therapeutic Classes

Fee for Service

Quarter 4, 2019 and Quarter 1, 2020

Top 10 Drug Classes by Claim Count - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,893	$2,548,418.73
SYMPATHOMIMETICS**	20,961	$2,807,735.43
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	16,384	$213,229.64
OPIOID COMBINATIONS**	15,035	$362,362.68
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,487	$308,527.83
CENTRAL MUSCLE RELAXANTS**	12,617	$220,373.93
HMG COA REDUCTASE INHIBITORS**	10,720	$344,538.32
DIBENZAPINES**	10,071	$388,075.94
OPIOID AGONISTS**	9,919	$558,844.39
ANTIANXIETY AGENTS - MISC.**	8,661	$132,523.75

Top 10 Drug Classes by Claim Count - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,197	$2,447,192.25
SYMPATHOMIMETICS**	19,162	$2,696,212.95
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,934	$202,486.36
OPIOID COMBINATIONS**	15,193	$415,419.46
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,512	$308,642.07
CENTRAL MUSCLE RELAXANTS**	12,345	$212,678.92
HMG COA REDUCTASE INHIBITORS**	10,426	$337,165.51
OPIOID AGONISTS**	9,946	$587,281.11
DIBENZAPINES**	9,449	$372,158.63
ANTIANXIETY AGENTS - MISC.**	8,021	$125,056.25

Top 10 Drug Classes by Paid Amount - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTIHEMOPHILIC PRODUCTS**	109	$13,174,399.95
ANTIRETROVIRALS**	1,901	$3,769,758.99
INSULIN**	4,909	$3,430,514.92
SYMPATHOMIMETICS**	20,961	$2,807,735.43
LOCAL ANESTHETICS - TOPICAL**	1,751	$2,591,835.47
ANTICONVULSANTS - MISC.**	26,893	$2,548,418.73
BENZISOXAZOLES**	5,801	$2,499,702.51
ANTIPSYCHOTICS - MISC.**	3,032	$2,451,959.51
QUINOLINONE DERIVATIVES**	5,086	$1,907,802.85
ANTINEOPLASTIC ENZYME INHIBITORS**	160	$1,863,515.08

Top 10 Drug Classes by Paid Amount - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTIHEMOPHILIC PRODUCTS**	122	$13,142,137.18
ANTIRETROVIRALS**	2,084	$3,657,346.12
INSULIN**	4,504	$3,121,575.79
SYMPATHOMIMETICS**	19,162	$2,696,212.95
ANTICONVULSANTS - MISC.**	26,197	$2,447,192.25
BENZISOXAZOLES**	5,529	$2,363,048.09
ANTIPSYCHOTICS - MISC.**	2,782	$2,238,249.53
QUINOLINONE DERIVATIVES**	4,969	$1,823,960.10
ANTINEOPLASTIC ENZYME INHIBITORS**	154	$1,658,911.72
LOCAL ANESTHETICS - TOPICAL**	1,632	$1,644,457.33

cDUR Quarterly Report

Client(s): 'NVM'
Carrier ID: NVM
Account(s): All
Group(s): All
Primary Start Date: January 1, 2020
Primary End Date: March 31, 2020

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	666,891	148,873	22.3%
Rejected	527,353	168,880	28.2%
Reversed	101,241	31,293	27.4%
Total	***1,295,485***	***349,046***	***25.1%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
44,324	**$5,902,849**	**25,748**	**$17,341,962**	**70,072**	**$23,244,810**	**70,072**	**$23,244,810**

cDUR Detailed Activity Summary:

Intervention Type	Total	Paid Rxs		Rejected Rxs		Reversed Rxs	
	Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions
Dosing/Duration (DOSECHEK)	53,087	42,739	80.5%	1,212	2.3%	9,136	17.2%
Drug-Drug Interaction (DDI-DTMS)	109,351	49,469	45.2%	53,108	48.6%	6,774	6.2%
Duplicate Therapy (DUPTHER)	103,205	46,825	45.4%	48,207	46.7%	8,173	7.9%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	22	11	50.0%	N/A	N/A	11	50.0%
Duplicate Rx (DUPRX)	82,198	9,806	11.9%	65,211	79.3%	7,181	8.7%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	41	23	56.1%	N/A	N/A	18	43.9%
Refill Too Soon	1,142	N/A	N/A	1,142	100.0%	N/A	N/A
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***349,046***	***148,873***	***42.7%***	***168,880***	***48.4%***	***31,293***	***9.0%***

cDUR Detailed Saving Outcomes Summary:

Intervention Type	Current		Accruing		Total		Total Year to Date	
	Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
Dosing/Duration (DOSECHEK)	1,319	$1,686,786	2,485	$11,678,614	3,804	$13,365,400	3,804	$13,365,400
Drug-Drug Interaction (DDI-DTMS)	4,001	$255,361	6,432	$1,251,707	10,433	$1,507,068	10,433	$1,507,068
Duplicate Therapy (DUPTHER)	4,945	$857,644	9,592	$3,324,997	14,537	$4,182,641	14,537	$4,182,641
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	1	$7	2	$7	3	$14	3	$14
Duplicate Rx (DUPRX)	32,985	$3,006,011	7,081	$1,055,025	40,066	$4,061,036	40,066	$4,061,036
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	11	$2,152	1	$27	12	$2,178	12	$2,178
Refill Too Soon	1,062	$94,887	155	$31,585	1,217	$126,473	1,217	$126,473
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***44,324***	***$5,902,849***	***25,748***	***$17,341,962***	***70,072***	***$23,244,810***	***70,072***	***$23,244,810***

Claims Summary:

Column Name	Description
Claim Status	The claims status associated with the RxCLAIM transaction: Paid, Reversed, Rejected •Paid Claims with CDUR edit(s) are those which had an override by a pharmacist •Rejected claims with CDUR edit(s) include both hard and soft rejects •Reversed claims with CDUR edit(s) include Paid claims which were reversed, originating with a message and an override by a pharmacist
Total Rxs	The total number of pharmacy claims with or without a cDUR edit
Total Interventions	The total number of pharmacy claims with at least one cDUR edit
% Total Rxs w/ Interventions	Percentage of all pharmacy claims which had a cDUR edit

cDUR Savings Outcomes Summary:

Column Name	Description
Current	Savings from CDUR interventions which occurred in the current period
Accruing	Savings from CDUR interventions which succeeded prior to the current reporting period, where savings continue to accrue in the current reporting period
Total	Total CDUR savings recognized in the current period (Current + Accruing)
Year To Date	Total CDUR savings recognized since the start of the current year
Successes	cDUR Interventions which resulted in Pharmacy Savings in the Current Period

Edit Type	Short Description	Long Description
ACTMAINT	Acute/Maintenance Dose Screening	Member is taking a medication at a higher dose than recommended based on acute daily use versus maintenance daily use.
ALLERCHK	Drug-Allergy Interaction Screening	Member is taking a medication to which he/she may be allergic.
DDI-DTMS	Drug-Drug Interaction Screening	Member is taking 2 interacting medications and/or medication classes.
DIAGCAUT	Drug-Disease screening using actual member disease profile	Member has a certain diagnosis (as determined by member disease profile) and is taking a medication that worsens the diagnosis.
DINFERRD	Drug-Disease screening using medication history as proxy for determining existing disease states	Member has a certain diagnosis (as determined by drug proxy) and is taking a medication that may worsen the member diagnosis.
DOSECHEK	Identifies if incoming claim exceeds recommended daily dose and/or recommended duration	Member is taking a medication for longer and/or at a higher dose than recommended.
DRUG_AGE	Drug-Age contraindication screening	Member is taking a medication that is not recommended for people of certain ages (pediatric and geriatric).
DRUG_SEX	Drug-sex contraindication screening	Member is taking a medication that is not recommended for his/her gender.
DUPRX	Exact GPI duplication screening	Member is taking 2 medications with the same ingredient.
DUPTHER	Drug class duplication screening	Member is taking 2 medications in the same drug class.
MEDLIMIT	Morphine Equivalent Dose Limit Screening	Member is taking opioids where the total cumulative daily dose exceeds the suggested morphine equivalent dose (MED).
REFILL	Refill Too Soon	Member tried refilling with medicagtion still left of hand from prior fill
THERDOSE	Therapeutic Dose Limits Screening	Member is taking medications where the total cumulative daily dose exceeds the FDA approved maximum dose for the medication.

Nevada Medicaid

Retro-DUR Activities
Fee for Service
Quarter 1, 2020

Date	Type	Sent	Responses	Prescribers	Recipients
Mar-20	Zolpidem Util for females	40	0	40	40