Therapeutic Class Overview
Smoking Cessation Agents

INTRODUCTION

- Tobacco use is cited as the chief preventable cause of illness and death in the United States (U.S.) and is responsible for approximately 480,000 deaths each year (*National Institute on Drug Abuse [NIDA] 2020*).
- Despite the well-established adverse health consequences (eg, cardiovascular disease, multiple types of cancer, pulmonary disease, adverse reproductive outcomes, exacerbation of chronic health conditions), an estimated 34.2 million adults in the U.S. (13.7% of the adult population) currently smoke cigarettes. Passive or secondary smoke increases the risk of these adverse health consequences for nonsmokers, and increases lung cancer risk by about 20% (*Centers for Disease Control and Prevention [CDC] 2019, Department of Health and Human Services [DHHS] 2014, Fiore et al 2008, NIDA 2020*).
- E-cigarettes are currently the most commonly used tobacco product among youth, with more than 3 million (19% to 21%) high school students and 7% of 8th grade students reporting e-cigarette use in the prior month (*CDC 2018, Monitoring the Future 2019, Miech et al 2019*). E-cigarette aerosols can contain nicotine and harmful chemicals and solvents. Youth who use e-cigarettes or other tobacco products are more likely to use other tobacco products such as cigarettes (*DHHS 2016*). In 2018, the U.S. Surgeon General declared e-cigarette use among youth an epidemic (*U.S Surgeon General 2018*).
  - Recently, the CDC has reported data showing that the additive, vitamin E acetate, in some e-cigarette products is linked to e-cigarette, or vaping, product use-associated lung injury (EVALI); with more than 2600 reported cases thus far (*CDC 2020*).
- Although a high proportion of individuals express interest in quitting (currently reported at 70%), only slightly more than half of smokers make an attempt to quit (55.1% in 2018), and far fewer are successful in quitting (7.5% in 2018). Less than one-third of smokers attempting to quit report utilizing proven cessation methods such as counseling and/or medication (*CDC 2019*).
- Although some individuals are able to quit unaided, strong evidence is available showing that smokers are significantly more likely to quit successfully if they use evidence-based counseling or medication treatment than if they try to quit without such aids. First-line Food and Drug Administration (FDA)-approved pharmacologic interventions include nicotine replacement therapy (NRT), bupropion hydrochloride (HCl) sustained-release (SR), and varenicline. All first-line therapies are indicated as aids to smoking cessation treatment (*Fiore et al 2008, Siu et al 2015*).
- Studies have compared the effects of the first-line pharmacotherapies when administered as monotherapy or combination therapy. Multiple systematic reviews and meta-analyses have also been published evaluating the safety and efficacy of pharmacotherapy as an aid to smoking cessation.
- Over-the-counter (OTC) NRT products include nicotine gum, lozenge, and patch. Prescription NRT products include nicotine nasal spray and nicotine inhalation system. Chantix (varenicline) is a prescription partial nicotine agonist that prevents nicotine stimulation of the dopamine system and decreases craving and withdrawal symptoms. Zyban (bupropion HCl SR) is a prescription dopamine/norepinephrine-reuptake inhibitor; its ability to enhance tobacco cessation is not fully understood. The above mentioned agents will be discussed in this review.
- Medispan Class: Smoking Deterrents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Chantix (varenicline)	-
Nicoderm CQ (nicotine extended-release) transdermal patch*	✔
Nicorette (nicotine polacrilex) gum*	✔
Nicorette (nicotine polacrilex) lozenge*	✔
Nicotrol (nicotine) inhalation system	-
Nicotrol NS (nicotine) nasal spray	-
Zyban (bupropion HCl sustained-release)†	✔

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

*OTC products
†Brand Zyban was discontinued, but a generic version remains available.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication*	Chantix (varenicline)	Nicoderm CQ (nicotine extended-release) transdermal patch	Nicorette (nicotine polacrilex) gum	Nicorette (nicotine polacrilex) lozenge	Nicotrol (nicotine) inhalation system	Nicotrol NS† (nicotine) nasal spray	Zyban (bupropion HCl SR)
To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking		✔	✔	✔			
As an aid to smoking cessation for the relief of nicotine withdrawal symptoms					✔	✔	
As an aid to smoking cessation treatment	✔						✔

*All tobacco cessation agents should be used as part of a comprehensive behavioral smoking cessation program.
†The safety and efficacy of the continued use of NICOTROL NS for periods longer than 6 months have not been adequately studied and such use is not recommended.

(Prescribing information: *Bupropion HCl SR 2019, Chantix 2019, Nicoderm CQ 2018, Nicorette gum 2018, Nicorette lozenge 2018, Nicotrol 2019, Nicotrol NS 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

Comparative Efficacy of Pharmacologic Treatments

- A systematic review of 54 systematic reviews/meta-analyses, sponsored by the Agency for Healthcare Research and Quality (AHRQ), found that behavioral and pharmacotherapy interventions improved rates of smoking cessation among the general adult population, alone or in combination (*Patnode et al 2015*).
  - NRT might increase smoking abstinence at 6 months follow-up or longer by 53% to 68% (risk ratio [RR] 1.60; 95% confidence interval [CI], 1.53 to 1.68; I^2 = 30%; N = 51,265), bupropion SR by 49% to 76% (RR 1.62; 95% CI, 1.49 to 1.76; I^2 = 18%; N = 13,728), and varenicline by 102% to 155% (RR 2.27; 95% CI, 2.02 to 2.55; I^2 = 63%; N = 6166) compared to placebo or no NRT.
  - Absolute cessation differences averaged 7% for NRT, 8.2% for bupropion SR, and 16% for varenicline.
  - No differences were found among NRT products (eg, patch, gum, lozenge).
  - Use of a combination of NRT products increased cessation rates more than the use of a single NRT product (20.6% vs 5%, respectively; RR 1.34; 95% CI, 1.18 to 1.51; I^2 = 34%; N = 4664).
  - Combined behavioral interventions and pharmacotherapy also increased cessation rates at ≥ 6 months after the start of treatment vs control groups (14.5% vs 8.3%, respectively; RR 1.82; 95% CI, 1.66 to 2.00; N = 15,021).
- A Cochrane review of 12 published Cochrane reviews (N = 101,804) demonstrated the efficacy of NRT, bupropion, and varenicline in improving the chances of quitting smoking. Based on network meta-analysis, the following findings were observed for sustained smoking cessation ≥ 6 months from the start of treatment (*Cahill et al 2013*):

- Both NRT (odds ratio [OR] 1.84; 95% CI, 1.71 to 1.99) and bupropion (OR 1.82; 95% CI, 1.60 to 2.06) were superior to placebo. Varenicline more than doubled the chances of quitting compared to placebo (OR 2.88; 95% CI, 2.40 to 3.47).
- Direct comparisons between bupropion and NRT suggested equal efficacy with no advantage for either treatment (OR 0.99; 95% CI, 0.86 to 1.13).
- Varenicline was shown to be superior to both NRT (OR 1.57; 95% CI, 1.29 to 1.91) and bupropion (OR 1.59; 95% CI, 1.29 to 1.96) monotherapy. However, varenicline was not more effective than combination NRT (OR 1.06; 95% CI, 0.75 to 1.46).
- Binary meta-analysis of the results demonstrated that bupropion combined with NRT was not more effective than NRT alone (RR 1.23; 95% CI, 0.67 to 2.26).

- Three systematic reviews/meta-analyses of randomized controlled trials (RCTs) found all pharmacologic treatments (ie, NRT, bupropion, varenicline) to be significantly more effective than controls in assisting with smoking cessation up to 12 months after the target quit date. Varenicline was the only pharmacotherapy that demonstrated consistent effectiveness over other treatment options (*Eisenberg et al 2008, Mills et al 2012, Wu et al 2006*).
- A large, multi-center, double-blind (DB), placebo-controlled (PC) and active-controlled (AC) RCT demonstrated the safety and efficacy of varenicline and bupropion vs nicotine patch and placebo in patients with psychiatric disorders. A total of 8144 patients (4116 in psychiatric cohort; 4028 in non-psychiatric cohort) were randomized in a 1:1:1:1 fashion to receive varenicline, bupropion, nicotine patch, or placebo for 12 weeks. The primary endpoint was incidence of moderate and severe neuropsychiatric events. The primary efficacy endpoint was smoking abstinence for weeks 9 to 12 (*Anthenelli et al 2016*).
  - In the psychiatric cohort, moderate and severe neuropsychiatric events were reported in 6.5% of patients in the varenicline group, 6.7% of the bupropion group, 5.2% of the nicotine patch group, and 4.9% of the placebo group. The varenicline and bupropion vs placebo risk differences (RD) for these neuropsychiatric events were 1.59 (95% CI, -0.42 to 3.59) and 1.78 (95% CI, -0.24 to 3.81), respectively. The RD for varenicline and bupropion vs nicotine patch were 1.22 (95% CI, -0.81 to 3.25) and 1.42 (95% CI, -0.63 to 3.46), respectively.
  - In the non-psychiatric cohort, moderate and severe neuropsychiatric events were reported in 1.3% of patients in the varenicline group, 2.2% of the bupropion group, 2.5% of the nicotine patch group, and 2.4% of the placebo group. The varenicline and bupropion vs placebo RD for these neuropsychiatric events were -1.28 (95% CI, -2.4 to -0.15) and -0.08 (95% CI, -1.37 to 1.21), respectively. The RD for varenicline and bupropion vs nicotine patch were -1.07 (95% CI, -2.21 to 0.08) and 0.13 (95% CI, -1.19 to 1.45), respectively.
  - Higher abstinence rates were achieved in varenicline-treated patients compared to all other treatment arms. Compared with placebo, the bupropion and nicotine patch groups also achieved higher abstinence rates.
  - The results of this trial did not indicate a significant increase in moderate or severe neuropsychiatric events in patients with or without psychiatric disorders treated with varenicline or bupropion relative to nicotine patch or placebo.
- A DB, triple-dummy, PC and AC, RCT (N = 8058) comparing the cardiovascular safety risk of smoking cessation treatments (varenicline, bupropion, NRT) found that the incidence of major adverse cardiovascular events (MACE) during treatment and follow-up was low (< 0.5%) and did not differ significantly by treatment. There were no significant differences for any drug vs placebo in terms of time to cardiovascular event, blood pressure, or heart rate (*Benowitz et al 2018*).
- A meta-analysis of 32 randomized, DB, PC trials evaluated sex differences between bupropion, transdermal nicotine (TN) and varenicline for smoking cessation (N = 14,398); 51% of patients were female. Overall, all medications improved quit rates vs placebo for both women and men. However, significant sex differences were evident when comparing varenicline vs TN and varenicline vs bupropion. For women, varenicline was more efficacious than TN (RR 1.41; 95% CI, 1.12 to 1.76) and bupropion (RR 1.38; 95% CI, 1.08 to 1.77). For men, outcomes were similar across all 3 medications. There were no differences in efficacy when comparing bupropion versus TN. Authors concluded that the advantage of varenicline over bupropion SR and TN is greater for women than men (*Smith et al 2017*).

Efficacy of Combination Therapy vs Monotherapy

- A DB, PC, RCT (N = 385) was conducted at a hospital-based outpatient clinic to evaluate the efficacy of varenicline and bupropion combination therapy vs varenicline alone for smoking cessation. Patients were given 12 weeks of treatment and were followed for 12 months. The combination group failed to demonstrate superiority vs the varenicline alone group in terms of prolonged abstinence at 12 months (OR 0.91; 95% CI, 0.50 to 1.64). Both treatment groups were superior to placebo ($p < 0.016$) (*Cinciripini et al 2018*).

- A large Phase 4, open-label (OL), RCT was conducted in 2 counties in Wisconsin to determine the comparative efficacy of nicotine patch (N = 241), varenicline (N = 424), and combination nicotine patch plus nicotine lozenge (combination NRT) (N = 421) on biochemically confirmed abstinence at 26 weeks. Pharmacotherapy was administered at standard doses for 12 weeks. Results demonstrated that there were no significant differences in point prevalence abstinence rates among the 3 groups at 26 weeks (nicotine patch, 22.8%; varenicline, 23.6%; and combination NRT, 26.8%) or at 52 weeks (nicotine patch, 20.8%; varenicline, 19.1%; and combination NRT, 20.2%). No significant treatment effects were found between groups for prolonged abstinence rate (nicotine patch 14.9%, varenicline 16.5%, combination NRT 15.4%) (*Baker et al 2016*).
- Another Phase 4, OL, RCT conducted at a single center in Canada evaluated the comparative smoking cessation effects of standard nicotine patch administered for 10 weeks (NRT; N = 245), extended use of nicotine patch plus nicotine gum or inhaler administered for up to 22 weeks (combination NRT; N = 245), and varenicline 1 mg twice daily administered for up to 24 weeks (N = 247). Overall, combination NRT and varenicline were found to enhance success in the early phases of quitting. Varenicline improved abstinence in the medium-term; however, there was no clear evidence that either varenicline or combination NRT increased quit rates in the long-term when compared to NRT monotherapy. No differences in continuous abstinence rates were observed between treatment groups from weeks 5 to 52 (10.0%, 12.4%, and 15.3% in the NRT, combination NRT, and varenicline groups, respectively). However, both combination NRT and varenicline had statistically significantly higher continuous abstinence rates over NRT monotherapy from weeks 5 to 10 (unadjusted OR 1.52; 97.5% CI, 1.00 to 2.30, and OR 1.58; 97.5% CI, 1.04 to 2.39, respectively), and varenicline had higher continuous abstinence rates over NRT at weeks 5 to 22 (unadjusted OR 2.01; 97.5% CI, 1.20 to 3.36) (*Tulloch et al 2016*).
- The efficacy of combination nicotine patch with other pharmacotherapy (ie, nicotine gum, nicotine inhaler, nicotine nasal spray, bupropion HCl SR) compared to monotherapy or placebo was evaluated in a meta-analysis of 5 RCTs (N = 2204). Abstinence rates were significantly higher with combination therapy than monotherapy at 3 months (39.0% vs 27.6%, respectively; RR 1.42; 95% CI, 1.21 to 1.67), 6 months (29.3% vs 19.1%, respectively; RR 1.54; 95% CI, 1.19 to 2.00), and 12 months (22.2% vs 14.3%, respectively; RR 1.58; 95% CI, 1.25 to 1.99). Adverse events (AEs) and adherence to combination therapy were similar to monotherapy and placebo (*Shah et al 2008*).
- A Cochrane systematic review of 63 studies (N = 41,509) comparing at least 2 NRT regimens found a higher rate of abstinence at 6 months with combination NRT therapy compared to monotherapy (RR 1.25, 95% CI, 1.15 to 1.36, 14 studies, 11,356 participants) *(Lindson et al 2019).*

Antidepressants

- A Cochrane systematic review of 90 RCTs (N > 27,000) assessed the efficacy of antidepressants in aiding long-term smoking cessation. Both bupropion and nortriptyline were more effective than placebo (bupropion: RR 1.62; 95% CI, 1.49 to 1.76; nortriptyline: RR 2.03; 95% CI, 1.48 to 2.78). There was no evidence of significant effects with other antidepressant therapies. Bupropion and nortriptyline appeared equally effective, although the comparison trended toward favoring bupropion (RR 1.30; 95% CI, 0.93 to 1.82). Bupropion had significantly lower abstinence rates compared to varenicline (RR 0.68; 95% CI, 0.56 to 0.83). There were no direct comparisons between nortriptyline and varenicline (*Hughes et al 2015*).

Nicotine Replacement Therapies

- A Cochrane systematic review of 136 studies (N = 64,640 in main analysis) found that all forms of NRT (gum, transdermal patch, intranasal spray, and sublingual tablets/lozenges) significantly increased the rate of smoking cessation compared to placebo or no NRT control. The RR for abstinence for any form of NRT compared to control was 1.55 (95% CI, 1.49 to 1.61). The effects were largely independent of the definition of abstinence, the intensity of additional support provided, or the setting in which the NRT was offered. In a subset of 6 trials in pregnant women, NRT had a statistically significant benefit on abstinence close to the time of delivery (RR 1.32; 95% CI, 1.04 to 1.69); however, the result was no longer statistically significant in the 4 trials that followed patients post-partum (*Hartmann-Boyce et al 2018*).
- Pooled results from a meta-analysis comparing long-term studies (2 to 8 years, weighted mean 4.3 years) of single-course NRT vs control (12 RCTs, N = 4792) found that the long-term benefit of NRT is modest, and tobacco dependence treatment might be better viewed as a chronic disorder requiring repeated episodes of treatment. Abstinence rates were similar after 1 year of follow-up (OR 2.13; 95% CI, 1.68 to 2.69) and after more than 1 year of follow-up (OR 1.99; 95% CI, 1.50 to 2.64). The overall relapse rate between 12 months and final follow-up was 30.0%. The relapse rate did not differ by time of final follow-up, suggesting that most relapses after 12 months occur in the

following 1 to 2 years. Due to relapse, the estimated overall net benefit of NRT over and above placebo declined from 10.7% after 1 year to 7.2% at a mean of 4.3 years of follow-up (*Etter et al 2006*).

Varenicline

- A recent Cochrane review of 42 studies (N = 27,537) evaluated the safety and efficacy of varenicline for smoking cessation (*Cahill et al 2016*).
  - Pooled data from 27 trials indicated that standard-dose varenicline (1 mg twice daily for 12 weeks) increased the chances of successful long-term smoking cessation between 2- and 3-fold compared to placebo (RR 2.24; 95% CI, 2.06 to 2.43).
  - Extended varenicline treatment beyond 12 weeks was well tolerated and demonstrated a clear benefit over placebo (RR 3.64; 95% CI, 2.81 to 4.72; 4 trials).
  - Similar to other systematic reviews/meta-analyses, varenicline demonstrated significantly greater efficacy over bupropion (RR 1.39; 95% CI, 1.25 to 1.54) and NRT (RR 1.25; 95% CI, 1.14 to 1.37).
- In a meta-analysis of 5 RCTs (N = 2292), longer courses of varenicline treatment significantly improved the likelihood of successful smoking cessation. A significant relationship was found between the length of exposure to varenicline and abstinence rates (β coefficient, 0.5% absolute increase in abstinence rate per week of exposure; 95% CI, 0.3 to 0.8%; $p < 0.0001$). The unadjusted abstinence rates for 6-, 12-, and 24-weeks of varenicline treatment were 14.4%, 22.4%, and 43.6%, respectively (*Lee et al 2008*).
- A meta-analysis of 3 RCTs (N = 904) found combination therapy with varenicline and NRT to be more effective than varenicline alone in achieving smoking abstinence before or at the end of treatment (44.4% vs 35.1%, respectively; OR 1.50; 95% CI, 1.14 to 1.97), and after the end of treatment (32.4% vs 23.1%, respectively; OR 1.62; 95% CI, 1.18 to 2.23). The incidence of AEs was similar between the 2 treatment groups. Patients receiving combination therapy reported slightly more nausea (28.4% vs 25.7%), insomnia (18.7% vs 15.4%), and abnormal dreams (13.6% vs 10.7%) vs varenicline monotherapy (*Chang et al 2015*).
- Varenicline has a warning for the potential for serious cardiovascular events to occur. Previous meta-analyses have provided conflicting results regarding these events. A recent meta-analysis of 38 RCTs (N = 12,706) found no difference in serious cardiovascular events with varenicline vs placebo (RR 1.03; 95% CI, 0.72 to 1.49). Findings were similar when comparing patients with and without cardiovascular disease (RR 1.04; 95% CI, 0.57 to 1.89; RR 1.03; 95% CI, 0.64 to 1.64, respectively). No difference was detected in all-cause mortality between the varenicline and placebo groups (RR 0.88; 95% CI, 0.5 to 1.52) (*Sterling et al 2016*).

CLINICAL GUIDELINES

U.S. Public Health Service – Treating Tobacco Use and Dependence (*Fiore et al 2008*)

- The combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. Therefore, whenever feasible and appropriate, both counseling and medication should be provided to patients trying to quit smoking.
- Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations for which there is insufficient evidence of effectiveness (ie, pregnant women, smokeless tobacco users, light smokers, and adolescents)
- All NRT, bupropion SR, and varenicline are considered first-line treatment options and reliably increase long-term smoking abstinence rates.
- Certain combinations of first-line medications have been shown to be effective smoking cessation treatments. Therefore, clinicians should consider using these combinations of medications with their patients who are willing to quit. Effective combination medications are:
  - Long-term (> 14 weeks) nicotine patch + other NRT (gum and spray)
  - Nicotine patch + nicotine inhaler
  - Nicotine patch + bupropion SR (only combination approved by the FDA)

U.S. Preventive Services Task Force (USPSTF) – Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women (*Siu et al 2015*)

- Clinicians should ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral and FDA-approved pharmacotherapy for cessation.
- Nonpregnant adults ≥ 18 years:
  - Pharmacotherapy and behavioral intervention should be provided for cessation.

  - Behavioral therapy alone or combined with pharmacotherapy substantially improves achievement of tobacco cessation.
  - Use of NRT, bupropion, or varenicline with or without behavioral therapy substantially improves achievement of tobacco cessation. Using 2 types of NRT moderately improves achievement of tobacco cessation over using 1 type. The addition of NRT to bupropion SR provides benefit over use of bupropion SR alone.
- Pregnant women ≥ 18 years:
  - Behavioral interventions should be provided for cessation.
  - Behavioral interventions substantially improve achievement of tobacco smoking abstinence, increase infant birthweight, and reduce risk for preterm birth.
  - There is inadequate or no evidence on the benefits of NRT, bupropion SR, or varenicline to achieve tobacco cessation in pregnant women or improve perinatal outcomes in infants; the balance of benefits and harms cannot be determined.

National Comprehensive Cancer Network (NCCN) – Smoking Cessation (*NCCN 2019*)
- Treatment plans for all patients should include a combination of motivational/behavioral strategies and pharmacotherapy. Behavioral strategies include brief counseling and ≥ 4 individual or group therapy sessions (preferred).
- The most effective pharmacotherapy options are varenicline and NRT. A trial of varenicline or combination NRT (transdermal patch plus lozenge, gum, or inhaler) for 12 weeks should be attempted as primary therapy, and this can be continued for 6 to 12 months if needed.
- Relapse can be managed by restarting the treatment used for primary therapy or trying the other therapy.
- Bupropion alone or in combination with NRT can be considered as a subsequent therapy option. Bupropion should not be used in patients with brain metastases.
- Varenicline-associated nausea should be carefully managed in patients with cancer, especially those receiving concurrent chemotherapy.

American Academy of Pediatrics – Clinical Practice Policy to Protect Children From Tobacco, Nicotine, and Tobacco Smoke (*Farber et al 2015)*
- Clinicians should ask about tobacco use, including e-cigarette use, during all visits with children or adolescents.
- Parent and caregiver tobacco use should also be addressed and tobacco dependence treatment offered.
- Adolescents who want to stop smoking should be offered tobacco dependence treatment, which can include pharmacotherapy (any medication that is FDA-approved for tobacco dependence in adults) for moderate to severe dependence.
- Electronic nicotine delivery devices (such as e-cigarettes) should not be offered to adolescents with tobacco dependence.
- Telephone/text quitline referral and other behavioral interventions can also be considered for adolescents.

American College of Cardiology (ACC) Expert Consensus Decision Pathway on Tobacco Cessation Treatment (*Barua et al 2018*)
- The pathway is a systematic stepwise guide for addressing cigarette smoking efficiently and effectively during a routine office-based appointment.
  1. Ask about and document every patient's tobacco use status and exposure to secondhand smoke at every visit using a standardized assessment method.
  2. Assess current smokers' degree of nicotine addiction, former smokers' risk of relapse, and all nonsmokers exposure to secondhand smoke.
  3. Advise all tobacco users to quit, emphasizing the personal benefits of cessation rather than the harms of continuing to smoke, and advise all nonsmokers to avoid secondhand smoke exposure.
  4. Offer and connect smokers to appropriate treatment options (prescribing pharmacotherapy and actively linking smokers to behavioral support available in their healthcare institution or in the community.
  5. Follow up with patients at subsequent visits to monitor smoking status and sustain engagement in smoking cessation treatments as needed.

- Pharmacotherapy should act synergistically with behavioral counseling to increase quit rates.
  - The first-line pharmacotherapy recommendations for smoking cessation, including in smokers with cardiovascular disease, are varenicline and combination NRT.
  - NRT monotherapy and bupropion are considered second-line options for patients with cardiovascular disease who are not able or willing to use first-line choices.

SAFETY SUMMARY

Boxed Warnings:

- Suicidality and antidepressant drugs: Although bupropion HCl SR (Zyban) is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin, Wellbutrin SR, and Wellbutrin XL. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. Patients of all ages who are started on antidepressant therapy should be monitored closely for worsening, and for emergence of, suicidal thoughts and behaviors.
- The FDA recently removed the boxed warning for serious mental health AEs from the Chantix and Zyban drug labels based on results from a large clinical trial. The risk of serious AEs on mood or behavior was found to be lower than previously thought. Although the risk of mental AEs in patients with current or history of mental illness is still present, most did not have serious consequences (ie, hospitalization). The benefits of smoking cessation outweigh the risks with these medications (*FDA Safety Communication 2016, FDA Safety Oversight Meeting 2017*).

Contraindications:

- Bupropion HCl SR is contraindicated in seizure disorders, history of anorexia or bulimia, or patients undergoing abrupt cessation of ethanol or sedatives; concurrent or recent (within 14 days) use of monoamine oxidase inhibitors (MAO-Is) is also contraindicated.
- Varenicline is contraindicated in patients with a known history of serious hypersensitivity or skin reactions to varenicline. There have been postmarketing reports of rare, potentially life-threatening skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients treated with varenicline. Patients should contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.
- Nicotine polacrilex lozenges contain soya. Patients who are allergic to soya should not use this formulation.

Warnings/Precautions:

- Serious neuropsychiatric reactions (eg, changes in mood [including depression and mania], psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide) have been reported in patients taking bupropion for smoking cessation and in patients taking varenicline. These events have occurred in patients with and without pre-existing psychiatric disease. Patients should be instructed to discontinue the drug and to contact a healthcare provider if they experience such AEs.
- Both bupropion HCl SR and varenicline have a risk of seizures. These medications should be used with caution in patients with a history of seizures or other factors that can lower the seizure threshold.
- Bupropion HCl SR can cause hypertension, precipitate a manic or hypomanic episode in patients with bipolar disorder or risk factors for bipolar disorder, and trigger an angle-closure attack in patients with angle-closure glaucoma.
- Nicotine can increase heart rate and blood pressure. The risk of nicotine replacement in patients with cardiovascular and peripheral vascular disease should be weighed against the benefits of including NRT in a smoking cessation program. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed. Nicotine inhaler/nasal spray generally should not be used in patients during the immediate post-myocardial infarction period, or in patients with serious arrhythmias or severe/worsening angina.
- NRT should be used with caution in patients with hyperthyroidism, hepatic or renal impairment, insulin-dependent diabetes, and patients with active peptic ulcer disease, as healing may be delayed.
- Nicotine nasal spray is not recommended for use in patients with chronic nasal disorders. Bronchospasm has been reported in patients with pre-existing asthma with use of both nicotine nasal spray and inhaler. Sustained use beyond 6 months with these products is not recommended.
- Varenicline may cause central nervous system (CNS) depression that may impair physical or mental abilities. Caution must be used when performing tasks that require mental alertness. Varenicline may also change the way patients react to alcohol; alcohol intake should be decreased until patients know how it is tolerated. Cases of somnambulism (sleep walking) have been reported with use of varenicline involving harmful behavior to self, others, or property.

- An evaluation of the cardiovascular risk with varenicline suggests that patients with underlying cardiovascular disease may be at increased risk; however, these concerns must be balanced with the health benefits of smoking cessation. A trial in patients with stable cardiovascular disease demonstrated that while cardiovascular events were infrequent overall, some nonfatal events were reported more frequently in patients treated with varenicline. All-cause and cardiovascular mortality was lower in patients treated with varenicline. A meta-analysis of 15 trials found an increased hazard ratio for MACE of 1.95, but the finding was not statistically significant. In a large postmarketing neuropsychiatric safety outcome trial, few MACE events occurred.
- Nausea is the most common AE (up to 30% incidence rate) reported in patients treated with varenicline. It has been generally described as mild or moderate and often transient; however, it may persist over several months for some patients. The incidence of nausea is dose-dependent; initial dose titration may be beneficial in reducing the occurrence of nausea, and dose reduction for patients with intolerable nausea should be considered.
- Efficacy of varenicline has not been demonstrated in pediatric patients. Use of varenicline is not recommended for patients ≤ 16 years of age.
- Pregnancy and Lactation
  - Available data have not suggested an increased risk for major birth defects following exposure to varenicline in pregnancy, compared with women who smoke. There are no data on the presence of varenicline in human milk; the benefits of breastfeeding should be considered along with the mother's clinical need for the drug and any potential AEs on the breastfed child or from the underlying maternal condition.
  - Women who are pregnant should be encouraged not to smoke. The use of NRT to aid in smoking cessation has not been adequately studied in pregnant women; nonpharmacologic treatments are recommended. The amount of nicotine in breast milk from replacement products varies; caution should be exercised when nicotine is administered to breast-feeding women (*Facts & Comparisons 2018*).
  - Bupropion HCl SR is pregnancy category C. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant smokers should be encouraged to attempt cessation using nonpharmacological approaches first. Bupropion and its metabolites are present in human milk; caution should be exercised when it is administered to a nursing woman.

AEs:

- The most common AEs (incidence ≥ 5%) for bupropion HCl SR are insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia.
- The most common AEs for nicotine polacrilex gum/lozenges are injury to mouth, teeth, or dental work; belching; increased salivation; mild jaw muscle ache; and sore mouth/throat.
- The most common AEs for the nicotine transdermal patch are transient and generally mild erythema, pruritus, or burning at the application site.
- The most common AEs for the nicotine inhaler and nasal spray include local irritation of the mouth, throat, or nose; cough; dyspepsia; and headache. Nasal irritation was reported by nearly all (94%) patients treated with nicotine nasal spray during the first 2 days in a PC trial. Both the frequency and severity of nasal irritation declined with continued use, but was still experienced by 81% of patients after 3 weeks of nicotine nasal spray treatment. Most patients rated nasal irritation as mild or moderate.
- The most common AEs (incidence ≥ 5%) for varenicline are nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Chantix (varenicline)	Tablets	Oral	Once daily for 3 days, then twice daily	Dosing should begin 1 week prior to quit date. Alternatively, varenicline can be initiated with a later quit date set between days 8 and 35 of treatment. An additional 12 weeks of treatment is recommended if successful cessation

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				is achieved after the first 12-week course to further increase the likelihood of long-term abstinence. Administer after eating and with a full glass of water. Dosage adjustment is recommended for severe renal impairment and end-stage renal disease (ESRD).
Nicoderm CQ (nicotine extended-release)	Transdermal patch	Transdermal	Once daily	The patch is designed to be worn for 24 hours and then removed. The used patch should be removed and a new one applied to a different site at the same time each day. Hands should be washed after application or removal of a patch. The patch should be applied to any hairless site, avoiding areas with cuts, breakouts, scars, oil, burns, or irritation. The patch should not be cut in half or into smaller pieces.
Nicorette (nicotine polacrilex)	Gum	Oral	Weeks 1 to 6: 1 piece every 1 to 2 hours; Weeks 7 to 9: 1 piece every 2 to 4 hours; Weeks 10 to 12: 1 piece every 4 to 8 hours Maximum: 24 pieces/day	Patients should chew nicotine gum slowly until a tingling sensation in the mouth occurs, then park gum between cheek and gum. When tingling is gone, begin chewing again until tingle returns and repeat process until tingle is gone (about 30 min). Eating and drinking should be avoided 15 min before using and while gum is in mouth. The gum should not be swallowed.
Nicorette (nicotine polacrilex)	Lozenge	Oral	Weeks 1 to 6: 1 lozenge every 1 to 2 hours; Weeks 7 to 9: 1 lozenge every 2 to 4 hours; Weeks 10 to 12: 1 lozenge every 4 to 8 hours Maximum: 5 lozenges/6 hours or 20	Patients should place the lozenge in the mouth and allow to slowly dissolve. The lozenge should occasionally be moved from one side of the mouth to the other until completely dissolved (about 20 to 30 minutes). Eating and drinking should be avoided 15 min before using and while lozenge is in mouth.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			lozenges/day	The lozenge should not be chewed or swallowed.
Nicotrol (nicotine)	Inhalation system (cartridge)	Inhaled	6 to 16 cartridges per day for up to 12 weeks, then gradual reduction of dose for 6 to 12 weeks Maximum: 16 cartridges/day	A cartridge is inserted into the inhaler before use; the patient should inhale deeply into the back of the throat or puff in short breaths. The nicotine in each cartridge is used up after about 20 minutes of active puffing.
Nicotrol NS (nicotine)	Nasal spray	Intranasal	Initial: 1 spray (0.5 mg) in each nostril 1 or 2 times/hour Maximum: 40 doses (80 sprays)	Patients should be encouraged to use at least the recommended minimum of 8 doses per day, as less is unlikely to be effective. Patients should not sniff, swallow or inhale through the nose as the spray is being administered. Patients should be advised to administer the spray with the head tilted back slightly Maximum recommended duration of treatment: 3 months
Zyban (bupropion HCl sustained-release)	Tablets	Oral	Once daily for 3 days, then twice daily	Tablets should be swallowed whole and should not be crushed, divided, or chewed. May be taken with or without food. Dosing should begin 1 week before quit date. Dose adjustment is recommended for moderate to severe hepatic impairment. Dosage adjustment should be considered for mild renal and hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Tobacco use is the primary avoidable cause of illness and death in the U.S., leading to approximately 480,000 deaths each year. Almost 50 million adults in the U.S. use tobacco on a regular basis. Cardiovascular disease, cancers, pulmonary disease, and adverse reproductive outcomes are all well-known adverse health consequences of tobacco use (*CDC 2019, Fiore et al 2008, NIDA 2020*).
- Less than 1 in 10 smokers are successful in quitting, but strong evidence indicates that smokers are significantly more likely to successfully quit if behavioral therapy and/or tobacco cessation medication is used. NRT, bupropion HCl SR, and varenicline are all effective first-line medication therapies. Nicotine gum, lozenges, and patches are available OTC.

Nicotine inhalation and nasal spray, bupropion SR, and varenicline are prescription products (*CDC 2017, Fiore et al 2008, Siu et al 2015*).

- Meta-analyses comparing NRT, bupropion SR, and varenicline have found all to be efficacious in aiding smoking cessation. Data suggest that varenicline monotherapy may be more effective than NRT or bupropion monotherapy (*Cahill et al 2013, Eisenberg et al 2008, Mills et al 2012, Patnode et al 2015, Wu et al 2006*).
- Meta-analyses have shown statistically significantly better abstinence rates in smokers using combination therapy with multiple NRT products or NRT plus bupropion SR or varenicline (*Chang et al 2015, Lindson et al 2019, Shah et al 2008, Stead et al 2012*).
- Bupropion HCl SR (Zyban), although only used as a smoking cessation therapy, shares a boxed warning with other antidepressant drugs that it may increase the risk of suicidal thoughts and behaviors in children, adolescents, and young adults. Bupropion is contraindicated in patients with seizure disorders.
- NRT can cause increased heart rate and blood pressure; risk vs benefit should be weighed in patients with cardiovascular and peripheral vascular disease. NRT should be used with caution in patients with hyperthyroidism, hepatic or renal impairment, insulin-dependent diabetes, and patients with peptic ulcer disease. The most common AEs are local irritation related to product application site and are typically mild in nature.
- Varenicline may cause CNS depression, neuropsychiatric effects, and an increased risk of cardiovascular events. Nausea is the most common AE and is typically dose-dependent.
- Current guidelines from the U.S. Public Health Service, USPSTF, NCCN, and the American Academy of Pediatrics recommend that health professionals encourage all patients to quit smoking and to provide behavioral therapy and/or FDA-approved tobacco cessation medication when appropriate. A combination of behavioral therapy with tobacco cessation medication is significantly more effective than monotherapy. NRT, bupropion HCl SR, and varenicline are all considered first-line and efficacious in adults (*Fiore et al 2008, Siu et al 2015, NCCN 2019, Farber et al 2015*). The American Academy of Pediatrics does not provide specific pharmacotherapy recommendations for tobacco cessation in adolescents but states that use of these products can be considered (*Farber et al 2015*).

REFERENCES

- Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *Lancet*. 2016;387:2507-2520.
- Baker TB, Piper ME, Stein JH, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *JAMA*. 2016;315(4):371-379.
- Barua, RS, Rigotti NA, Benowitz NL et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment. *JACC*. 2018;72(25):3332-3365. http://www.onlinejacc.org/content/accj/72/25/3332.full.pdf. Accessed January 13, 2020
- Benowitz NL, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: A randomized clinical trial. *JAMA Intern Med*. 2018;178(5):622-631.
- Bupropion hydrochloride SR [package insert], Parsippany, NJ: Actavis Pharma, Inc.; July 2019.
- Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;5:CD006103.
- Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;(5):CD009329.
- Centers for Disease Control and Prevention. Tobacco product use among adults – United States, 2018. *Morbidity and Mortality Weekly Report.* 2019;67(44):1225-1232.
- Centers for Disease Control and Prevention. Quitting smoking among adults – United States 2000-2015. *Morbidity and Mortality Weekly Report*. 2017;65(52):1457-64.
- Centers for Disease Control and Prevention. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students — United States, 2011–2018. *Morbidity and Mortality Weekly Report.* 2018;67(45)1276-1277.
- Centers for Disease Control and Prevention. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Updated January 28, 2020. Accessed February 6, 2020.
- Chang PH, Chiang CH, Ho WC, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689.
- Chantix [package insert], New York, NY: Pfizer, Inc.; December 2019.
- Cinciripini PM, Minnix JA, Green CE, et al. An RCT with the combination of varenicline and bupropion for smoking cessation: clinical implications for front line use. *Addiction*. 2018 Apr 21. doi: 10.1111/add.14250.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2019. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 13, 2020.
- Eisenberg MJ, Filion KB, Yavin D, et al. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *CMAJ*. 2008;179(2):135-144.
- Etter JF, Stapleton JA. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. *Tob Control*. 2006;15(4):280-285.
- Facts & Comparison Web site. https://fco.factsandcomparisons.com/. Accessed January 13, 2020.

- Farber HJ, Walley SC, Groner JA, Nelson KE; Section on Tobacco Control. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. *Pediatrics*. 2015;136(5):1008-17. doi: 10.1542/peds.2015-3108.
- Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Rockville, MD: US Department of Health and Human Services, Public Health Service; 2008. http://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf. Accessed January 13, 2020.
- Food and Drug Administration: Drug Safety Oversight Board Meeting - March 16, 2017. https://www.fda.gov/about-fda/center-drug-evaluation-and-research/drug-safety-oversight-board-meeting-march-16-2017. Accessed January 13, 2020.
- Food and Drug Administration Drug Safety Communication. FDA revises description of mental health side effects of the stop smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. December 16, 2016. Last updated March 8, 2018. http://www.fda.gov/Drugs/DrugSafety/ucm532221.htm. Accessed January 13, 2020.
- Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018;5:CD000146.
- Hughes JR, Stead LF, Harmann-Boyce J, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2015;(1):CD000031.
- Lee JH, Jones PG, Bybee K, et al. A longer course of varenicline therapy improves smoking cessation rates. *Prev Cardiol*. 2008;11(4):210-214.
- Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations, and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2019;4:CD013308. doi: 10.1002/14651858.CD013308.
- Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Adolescent vaping and nicotine use in 2017-2018 - U.S. national estimates. *N Engl J Med*. 2019;380(2):192-193. doi: 10.1056/NEJMc1814130.
- Mills EJ, Wu P, Lockhart I, et al. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. *Ann Med*. 2012;44(6):588-597.
- Monitoring the Future. National Adolescent Drug Trends in 2019. http://monitoringthefuture.org/pressreleases/19drugpr.pdf. Accessed January 13, 2020.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Smoking Cessation. Version 2.2019. Updated May 6, 2019. https://www.nccn.org/professionals/physician_gls/pdf/smoking.pdf. Accessed January 13, 2020.
- National Institute on Drug Abuse (NIDA). Research report series – Tobacco, nicotine, and e-cigarettes. U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; modified January 2020. https://www.drugabuse.gov/node/pdf/1344/tobacco-nicotine-and-e-cigarettes Accessed January 13, 2020.
- Nicoderm CQ [package insert], Warren, NJ: GSK Consumer Healthcare; October 2018.
- Nicorette gum [package insert], Warren, NJ: GlaxoSmithKline Consumer Healthcare; December 2018.
- Nicorette lozenge [package insert], Warren, NJ: GSK Consumer Healthcare; April 2018.
- Nicotrol [package insert], New York, NY: Pfizer, Inc.; September 2019.
- Nicotrol NS [package insert], New York, NY: Pfizer, Inc.; September 2019.
- Office of the U.S. Surgeon General. Surgeon General's Advisory on E-cigarette Use Among Youth. 2018. https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf. Accessed January 13, 2020.
- 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; 2019. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 13, 2020
- Patnode CD, Henderson JT, Thompson JH, et al. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;163(8):608-621.
- Shah SD, Wilken LA, Winkler SR, et al. Systematic review and meta-analysis of combination therapy for smoking cessation. *J Am Pharm Assoc*. 2008;48(5):659-665.
- Siu AL; U.S. Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163(8):622-634.
- Smith PH, Weinberger AH, Zhang J. Sex Differences in Smoking Cessation Pharmacotherapy Comparative Efficacy: A network meta-analysis. *Nicotine Tob Res*. 2017:19(3):273-281. doi: 10.1093/ntr/ntw144.
- Sterling LH, Windle SB, Filion KB, et al. Varenicline and adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2016;5:e002849.
- Tulloch HE, Pipe AL, Els C, et al. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. *BMC Medicine*. 2016;14:80.
- U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General—executive summary. Atlanta, GA: USDHHS, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Fact_Sheet_508.pdf. Accessed January 13, 2020.
- U.S. Department of Health and Human Services. The health consequences of smoking – 50 years of progress: A report of the Surgeon General. Atlanta, GA: USDHHS, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf. Accessed January 13, 2020.
- Wu P, Wilson K, Dimoulas P, et al. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. *BMC Public Health*. 2006;6:300.

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