Therapeutic Class Overview
Anti-Migraine agents, miscellaneous

INTRODUCTION

- Migraine is a disabling, episodic, primary headache disorder. Worldwide, it affects over 1 billon people and is considered the leading cause of disability in people younger than 50 years old. Individuals with a family history of migraine are more susceptible to developing them, and female sex is a risk factor of migraines that can persist into adulthood; in general migraine headaches are more common in adult women than men (17% vs 6%) *(Ashina et al 2021*, *Cutrer et al 2020, International Headache Society [IHS] 2018, Oskoui et al 2019).*
- Migraines are categorized into 2 types: with aura or without aura. Migraines without aura are more common and account for approximately 75% of cases (*Cutrer et al 2020, IHS 2018).*
  - Migraine attacks typically last between 4 and 72 hours in adults, and usually progress through 4 phases: the prodrome, the aura (occurring in approximately 25% of individuals), the headache, and the postdrome.
  - Factors that may trigger a migraine can include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame.
- Tension-type headaches (TTH) is the most prevalent type of headache, affecting 30 to 78% of the general population, and is one of the most common reasons why individuals purchase over the counter analgesics. TTH can be further categorized into episodic (frequent or infrequent) and chronic types; common features include mild to moderate intensity, bilateral pressing or tightening (non-pulsating), and usually does not cause nausea, vomiting, photophobia, phonophobia that is commonly seen with migraines (*IHS 2018, Taylor 2020[a], Taylor 2020[b]*).
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen [APAP]), and moderate to severe attacks are treated more migraine specific agents including triptans, calcitonin gene-related peptide (CGRP) antagonist or other agents. The use of ergot alkaloids has been largely displaced with the advent of triptans for acute treatment (*Smith 2021*, *Tfelt-Hansen 2013*).
- The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, aspirin [ASA]) followed by combination analgesics containing caffeine plus a simple analgesic. The efficacy of the simple analgesics tends to decrease with increasing frequency of the headaches (*Taylor 2020[b], Bentsen et al 2010*).
- Avoiding medication overuse headache (MOH) is an important goal of acute therapy and can occur when primary headache disorders (eg, migraine, tension-type) have been treated with excessive amounts of acute symptomatic medications. The risk of developing MOH appears to be highest with opioids, butalbital-containing combination analgesics, and analgesic-caffeine combinations; thus guidelines recommend against their use due to this (*Bendtsen et al 2010, Garza 2019, Silberstein and McCrory et al 2001, Smith 2021*).
  - In order to prevent the development of MOH, most acute medications should be limited to less than 10 days per month (or less than 15 days per month for ASA, APAP, and NSAIDs), and preventive therapies should be used as the mainstay in patients with frequent headaches.
- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies, which may be in part due to insufficient outcomes reporting in early trials and inconsistencies in demonstrating statistically significant differences in headache relief, and the lack of more recent clinical trials (*Tfelt-Hansen 2000, Silberstein and McCrory 2003)*. Additionally, ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism, and caffeine enhances its absorption; levels are slightly higher with rectal administration. Similarly, dihydroergotamine (DHE) also goes through extensive first pass metabolism, thus intranasal (IN) and intravenous (IV) administration bypass this and can deliver adequate plasma concentrations (*Silberstein and McCrory 2002*).
- Reyvow (lasmiditan) is a first in class 5-hydroxytryptamine (5-HT)1F receptor agonist for acute treatment of migraine attacks (triptans are 5-HT 1b/1d agonists) approved in 2019 by the Food and Drug Administration (FDA). This newer agent may play a role in patients with cardiovascular (CV) contraindications to triptans due to lack of vasoconstrictor activity (*AHS 2019*). In January 2021, the Drug Enforcement Agency (DEA) published a final rule placing lasmitidan as a Schedule V drug based on human abuse potential studies demonstrating significantly higher scores for drug liking, euphoric mood and feelings of relaxation (*Reyvow prescribing information 2021*).

- The focus of this overview will be migraine treatments including ergot alkaloids, butalbital combination products and Reyvow (lasmiditan). Injectable formulations have been excluded from this review. Codeine containing combination products are reviewed in the short acting opioids TCO.
- Medispan classes: Ergot combinations; Migraine products – ergotamine, dihydroergotamine; Analgesic combinations; Selective serotonin agonists 5-HT(1F)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cafergot (ergotamine/caffeine) tablets	✔
Migergot (ergotamine/caffeine) rectal suppository	-
Ergomar (ergotamine tartrate) sublingual tablets	-
Migranal (dihydroergotamine mesylate) nasal solution	✔
Allzital, Bupap, Tencon (butalbital/APAP) tablets or capsules	✔
Fioricet, Vtol LQ (butalbital/caffeine/APAP) capsules or oral solution	✔
Fiorinal (butalbital/caffeine/ASA) tablets	✔
Reyvow (lasmiditan) tablets	-

Abbreviations: APAP = acetaminophen, ASA = aspirin

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cafergot (ergotamine/ caffeine)	Migergot (ergotamine/ caffeine)	Ergomar (ergotamine tartrate)	Migranal (dihydroergotamine mesylate)	Allzital, Bupap, Tencon (butalbital/APAP) *	Fioricet, Vtol LQ (butalbital/caffeine/ APAP) *	Fiorinal (butalbital/ caffeine/ASA)	Reyvow (lasmiditan)
Therapy to abort or prevent vascular headache (eg, migraine, migraine variants, or so-called "histaminic cephalalgia").	✔	✔	✔					
Acute treatment of migraine headaches with or without aura.				✔				✔ †
For the relief of the symptom complex of tension (or muscle contraction) headache					✔	✔	✔	

Abbreviations: APAP = acetaminophen, ASA = aspirin

Note: Safety and effectiveness of butalbital-containing products have been established in children aged 12 years and older.

* Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

† Limitation of use: not indicated for the preventative treatment of migraine.

(*Prescribing information: Allzital 2020, Bupap 2020, Cafergot 2019, Migergot 2019, Ergomar 2020, Fioricet 2021, Fiorinal 2018, Vtol LQ 2019, Migranal 2019, Tencon 2017, Reyvow 2021*)

- 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

Ergot alkaloids

- Currently, ergotamine can be used in patients with frequent, moderate migraine but have been found to be less effective than triptans; in 3 head-to-head randomized controlled trials (RCTs), oral triptans (sumatriptan, eletriptan, and rizatriptan) were superior to oral ergotamine 2 mg plus caffeine 200 mg for quicker onset of headache relief and pain freedom at 2 hours . Sumatriptan, however was associated with higher incidence of headache recurrence at 48 hours (*Christie et al 2003, Diener et al 2002, The Multinational Oral Sumatriptan and Caferget Comparative Study Group 1999, Worthington et al 2013).* An early comparator trial demonstrated non-inferiority of ergotamine vs other migraine treatments such as naproxen, but with more adverse effects (AEs) such as nausea (*Sargent et al 1988*).
- A crossover (XO), double-blind trial (DB; N = 272) compared almotriptan vs ergotamine plus caffeine for acute migraine therapy; The primary endpoint was the proportion of patients achieving pain freedom at 2 hours. Patients were instructed to treat 2 migraine attacks, 1 with almotriptan 12.5 mg and the other with ergotamine 2 mg plus caffeine 200 mg. Rescue medication could be used 2 or more hours after treatment with the study drug for persistent moderate to severe pain and recurrence medication (the study medication for that attack) was allowed for patients who initially responded to the study medication but experienced a recurrence or worsening of their migraine during the first 48 hours after taking the study medication (*Láinez et al 2007*).
  - Treatment with almotriptan was associated with a significantly greater proportion of patients achieving pain freedom at 2 hours vs ergotamine plus caffeine (20.9% vs 13.7%; $p < 0.05$).
  - The XO design also assessed the benefit of one treatment over the other demonstrating that of the 20.9% who achieved pain freedom at 2 hours with almotriptan, 29% also responded to ergotamine plus caffeine; of the 13.7% who achieved pain freedom at 2 hours with ergotamine plus caffeine, 44% responded to almotriptan.
  - The study was not powered to detect the differences in safety between almotriptan vs ergotamine plus caffeine.
- A network meta-analysis (NMA) of 141 RCTs (7 studies including ergotamines) evaluated the comparative tolerability of various treatments including triptans, NSAIDs, and ergotamines, in any combination with or without caffeine or barbiturates for acute migraine. The primary outcomes were any AE, treatment-related AEs, and serious AEs. Overall, triptans and ergotamine were both associated with higher odds of any AE compared with NSAIDs, while tolerability profiles were mixed and comparable across various treatments (*Thorlund et al 2017*).
- DHE (Migranal) IN was shown to be effective in 4 RCTs. Patients treated a single moderate to severe migraine headache with a single dose of DHE IN (or placebo) and assessed pain severity over the 24 hours. Following treatment, the percentage of patients achieving headache response (rather than pain freedom) was reported at 2 hours as significant in Study 1 ($p < 0.001$) and at 4 hours in Studies 2 ($p < 0.01$), 3 ($p < 0.001$) and 4 ($p < 0.001$) (*Migranal prescribing information 2019*).
  - An analysis of 4 RCTs comparing DHE IN to placebo found a statistically significant effect size in favor of DHE (0.34; 95% confidence interval [CI], 0.10 to 0.57). This is particularly important for patients with moderate to severe attacks who are unable to tolerate oral medications due to nausea and vomiting (*Silberstein and McCrory 2003).*
  - A systematic review (SR) and meta-analysis (MA) evaluated the use of sumatriptan IN for acute migraine attacks. One study was compared to DHE IN in terms of safety and found no significant difference between both groups in terms of the incidence of all AEs within 24 hours ($p = 0.97$) or withdrawal due to AEs ($p = 0.30$) (*Menshawy 2018*).
- Several comparative effectiveness studies have evaluated the efficacy of triptans vs ergot derivatives for the acute treatment of migraines.
  - In a multicenter, DB, double placebo, XO study compared sumatriptan subcutaneous (SC) to DHE IN and found that sumatriptan was significantly better at providing both headache relief at 2 hours and resolution ($p < 0.001$ for both endpoints). However, more AEs were reported with sumatriptan SC (43%) vs DHE IN (22%) and fewer patients experienced headache recurrence with DHE IN (31% vs 17% with sumatriptan) (*Touchon et al 1996, Worthington et al 2013*).
  - Two Cochrane reviews evaluated sumatriptan (SC and IN) to DHE nasal spray. Results of the included studies demonstrated a higher proportion of patients being pain free at 2 hours with sumatriptan SC vs DHE nasal spray, while the efficacy data comparing sumatriptan IN to DHE nasal spray was deemed unusable. Overall, there was insufficient data available to carry out pooled analyses for any outcomes of interest to draw firm conclusions regarding efficacy between treatments (*Derry et al 2012[a], Derry et al 2012[b]).* One SR considered the 2 Cochrane reviews,

among other individual studies and found DHE IN has variable to superior efficacy vs placebo in acute migraine; however, it was less effective then IN or SC sumatriptan (*Worthington et al 2013*).

Butalbital combinations – Fioricet (butalbital/caffeine/APAP) and Fiorinal (butalbital/caffeine/ASA)

- Recent clinical trials evaluating butalbital combination products (eg, butalbital/caffeine/APAP and butalbital/caffeine/ASA) for TTH are not available.
- One study has evaluated the efficacy of butalbital-containing agent for migraine headaches vs placebo and FDA-approved anti-migraine triptan medication. A Phase 3 RCT in 503 patients (88% were currently using a butalbital-containing drug) with migraine headache that severely impacted their life, directly compared Fioricet vs sumatriptan-naproxen vs placebo. The primary endpoint was the percentage of treated attacks with sustained pain free (SPF) response 2 to 24 hours after treatment with sumatriptan-naproxen vs Fioricet. SPF was defined as being pain-free from 2 through 24 hours after initial dosing without return of migraine pain or use of any rescue medication. Results demonstrated no difference in the primary endpoint between Fioricet vs sumatriptan-naproxen (6% vs 8%; OR, 1.3; p = 0.378). However, when each drug was compared to placebo, sumatriptan-naproxen was shown to have better pain relief compared to Fioricet for the secondary endpoints of pain-free, pain relief, migraine-free, complete symptom-free, and pain-free with relief of nausea, photophobia, phonophobia, and sinus/facial pain at most time points (*Derosier et al 2011, Worthington et al 2013*).

Reyvow (lasmiditan)

- The efficacy of lasmiditan in the acute treatment of migraine with or without aura was demonstrated in 2 Phase 3, DB, placebo controlled (PC) RCT trials, SAMURAI and SPARTAN (*Kuca et al 2018*, *Goadsby et al 2019*). Both studies included patients with CV risk factors, but SPARTAN included patients with known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. The efficacy of lasmiditan was evaluated in terms of pain freedom (defined as a reduction of moderate or severe headache pain to no pain) and Most Bothersome Symptom (MBS) freedom (defined as the absence of the self-identified MBS [photophobia, phonophobia, or nausea]) at 2 hours compared to placebo (*Reyvow Prescribing Information 2020*). In both studies, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo.
  - In SAMURAI (N = 1856), lasmiditan pain freedom at 2 hours dosing (200 mg: 32.2%; OR, 2.6, 95% CI, 2.0 to 3.6; p < 0.001; lasmiditan 100 mg: 28.2%; OR 2.2, 95% CI, 1.6 to 3.0; p < 0.001) vs placebo (15.5%).
    - Freedom from MBS (lasmiditan 200 mg: 40.7%; OR, 1.6; 95% CI, 1.3 to 2.1; p < 0.001; lasmiditan 100 mg: 40.9%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001) vs placebo (29.5%).
  - In SPARTAN (N = 3005), lasmiditan pain freedom at 2 hours (lasmiditan 200 mg: 38.8%; OR, 2.3; 95% CI, 1.8 to 3.1; p < 0.001; lasmiditan 100 mg: 31.4%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001; lasmiditan 50 mg: 28.6%, OR, 1.5; 95% CI, 1.1 to 1.9; p = 0.003) vs placebo (21.3%),
    - Freedom from MBS (lasmiditan 200 mg: 48.7%, OR, 1.9; 95% CI, 1.4 to 2.4; p < 0.001; lasmiditan 100 mg: 44.2%; OR, 1.6; 95% CI, 1.2 to 2.0; p < 0.001; 50 mg: 40.8%; OR, 1.4; 95% CI, 1.1 to 1.8; p = 0.009) vs placebo (33.5%).
- GLADIATOR was an open label extension trial that randomized 2116 patients from SAMURAI and SPARTAN to receive lasmiditan 100 mg or 200 mg with the goal of evaluating long-term safety and efficacy (up to 1 year of intermittent use). A total of 962 patients (48.6%) reported ≥ 1 treatment emergent AE including dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%), similar to those in the pivotal trials. Dizziness was the most common AE leading to discontinuation (*Brandes et al 2019*).
- An analysis evaluated the safety and efficacy of a second dose of lasmiditan for rescue or headache recurrence found some evidence of efficacy when taken for headache recurrence, but there was no clear benefit of a second dose for rescue treatment (*Loo et al 2019*).
- A SR and MA of 3 RCTs (N=4,506) evaluated the safety and efficacy of lasmiditan for acute treatment of migraine. Overall, lasmiditan was associated with a significantly increased rate of patients experiencing pain freedom at 2 hours post-dose vs placebo (31.6% vs 17.55%), and freedom from MBS at 2 hours (42.82% vs 30.38%). However, lasmiditan was associated with higher rates of fatigue, paresthesia, and somnolence (*Yang et al 2020*). Another SR and MA of 4 RCTs (N = 4,960) concluded that while lasmiditan is effective for acute treatment of migraine, it is associated with a higher incidence of central nervous system (CNS) related side effects including dizziness, nausea, fatigue, paresthesia and somnolence (p < 0.00001 for all AEs) (*Hou et al 2020*).

- An Institute for Clinical and Economic Review (ICER) NMA of 33 RCTs evaluated the safety and efficacy of lasmiditan and oral CGRP antagonists (rimegepant and ubrogepant) for acute treatment of migraine to each other, placebo, and triptans. Results from PC clinical trials indicate that lasmiditan, rimegepant and ubrogepant decrease symptoms of migraine attacks (pain, phonophobia, photophobia, or nausea) and improve function compared to placebo at 2 hours, but all interventions showed lower odds of achieving pain freedom compared to triptans. Additionally, while similar rates of efficacy were demonstrated between the newer agents, lasmiditan had significantly higher rates of dizziness and discontinuation (*Atlas et al 2020*).

- The Agency for Healthcare Research and Quality (AHRQ) evaluated the comparative effectiveness of various pharmacotherapies used for the treatment of migraine headaches (*Halker Singh et al 2020*). Sixteen RCTs with 2,615 patients specifically studied the efficacy of ergotamine, with or without caffeine, as well as ergotamine vs placebo or lidocaine. Endpoints included pain free or pain relief at 2 hours, pain scale at 2 hours, restored function at 1 day, pain free at 1 day, pain relief at 1-day, sustained pain free at 1 week, and sustained pain relief at 1 week. Compared to placebo, DHE IN (2 mg and 3 mg) was more likely to lead to pain free and restore function at 2 hours and 1 day. Additionally, while compared to placebo, ergotamine plus caffeine probably improves pain relief at 2 hours, but a number of RCTs failed to demonstrate significant difference in headache relief compared to placebo and was associated with more AEs, mirroring early trials.
  - Five RCTs evaluated the efficacy of lasmiditan and demonstrated probable improvement in pain relief at 2 hours and increased likelihood of being pain free at 2 hours, 1 day, 1 week, and restored function vs placebo. However, serious gastrointestinal and neurological AEs were more common with lasmiditan vs placebo.

CLINICAL GUIDELINES

- The 2019 American Headache Society (AHS) position statement on integrating new migraine treatments (*AHS 2019*) recommends the use of NSAIDs, non-opioid analgesics, APAP, or caffeinated analgesic combinations for acute treatment of mild to moderate migraine attacks. For moderate to severe attacks, the guidelines suggests DHE or triptans that respond poorly to NSAIDs or caffeinated combination products.
  - Non-oral formulations are recommended if severe nausea or vomiting are associated with a migraine attack. This can include sumatriptan (IN or inhaled), ketorolac (IN or intramuscular), or DHE (IN or SC).
  - The guidelines indicate that emerging acute treatments for migraine headache such as the CGRP antagonists indicated for acute use, and the selective 5-HT_{1F} receptor agonist (lasmiditan) do not have vasoconstrictive effects; therefore, they may play a role in patients with CV contraindications to triptans. It is recommended that patients be eligible for these newer agents if they have contraindications to the use of triptans or have failed to respond to or tolerate ≥ 2 oral triptans.
  - To avoid medication overuse, patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 to 3 headache days per week, and if exceeding this limit, should be offered preventative treatment.
- The 2019 American Academy of Neurology and AHS guideline for the acute symptomatic treatment of migraine in children and adolescents (*Oskoui et al 2019*) recommends the use of ibuprofen, APAP (in children and adolescents) and triptans (mainly in adolescents) for the relief of migraine pain. Ergots alone have not been studied in children.
- The 2019 European Headache Federation aids to management of headache disorders in primary care (2nd edition) recommends a stepwise approach to treatment. This includes treating 3 attacks at each step before proceeding to the next (*Steiner et al 2019*).
  - Step 1: non-opioid analgesic plus an antiemetic (when needed).
    - Opioids are considered ineffective for migraine, and barbiturates (eg, butalbital) have no place in migraine treatment.
  - Step 2: Triptans; limited to ≤ 10 days per month.
    - Domperidone 10 mg can be added for nausea, and nasal spray or SC formulations can be used when vomiting is present.
    - ergotamine is considered a poor substitute for triptans due to low and unpredictable bioavailability, which impairs efficacy, and poor tolerability. It is no longer recommended for routine use.
  - Treatment of relapse: a repeat dose of triptan may be used, and any patient with migraine who is not well controlled on acute therapy should be offer prophylaxis in addition to acute medication.

- The 2013 Canadian Headache Society (CHS) guideline for acute drug therapy for migraine indicates that ergotamine use is problematic in migraine because of poor oral absorption, vasoconstrictive side effects, and the frequent occurrence of dose limiting side effects such as nausea, which make it difficult to achieve a therapeutic dose in patients. Thus, ergotamine is not recommended routinely for acute migraine pain. Additionally, the guideline strongly recommends avoiding the use of butorphanol and butalbital containing medications. Intranasal or SC DHE can be considered for acute treatment of moderate to severe attacks (*Worthington et al 2013*).
- The 2010 EFNS guideline for the treatment of tension headache (*Bendtsen et al 2010*) recommends the use of simple analgesics (eg, APAP, ASA, ibuprofen, naproxen, ketoprofen, diclofenac) for mild to moderate TTH. Second-line treatment includes a simple analgesic plus caffeine. The guideline recommends against the use of combination products with codeine or barbiturates due to the increased risk of developing MOH. Additionally, triptans most likely do not have a clinically relevant effect in patients with TTH and cannot be recommended.
- The 2009 European Federation of Neurological Societies (EFNS) guideline for the treatment of migraine (*Evers et al 2009)* recommends the use of NSAIDs and triptans for acute treatment of migraine attacks. In very severe attacks, IV ASA or SC sumatriptan are drugs of first choice.

SAFETY SUMMARY

- Cafergot, Migergot, Ergomar (ergotamine/caffeine)
  - **Boxed warning**: Co-administration with potent cytochrome P450 (CYP) 3A4 inhibitors can lead to elevated serum levels of ergotamine tartrate increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications:
    - Pregnancy and nursing: Category X, potential to cause fetal harm, oxytocic effects
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
  - Warnings and precautions
    - Co-administration with potent CYP3A4 inhibitors can lead to serious AEs.
    - Ergotism (intense arterial vasoconstriction), fibrotic complications with long term, continuous use.
    - Drug abuse and dependence with long term use.
  - AEs
    - Vasoconstrictive complications, nausea, vomiting, rectal or anal ulcers (from suppository overuse), local edema or itching (suppository use).
  - Key drug interactions: Potent CYP3A4 inhibitors (ie, macrolide antibiotics, protease inhibitors, fluconazole, grapefruit juice, fluoxetine)

- Migranal (dihydroergotamine mesylate)
  - **Boxed warning**: Co-administration with potent CYP3A4 inhibitors (ie, protease inhibitors, macrolide antibiotics) can lead to elevated serum DHE levels increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications
    - Co-administration with potent CYP3A4 inhibitors
    - Ischemic heart disease, coronary artery vasospasm (including Prinzmetal's variant angina),
    - Do not use within 24 hours of taking sumatriptan, ergotamine-containing or ergot-type medications, or methysergide.
    - Should not be used in patients with hemiplegic or basilar type migraines.
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
    - Pregnancy and nursing: Potential to cause fetal harm, oxytocic effects
    - Should not be used with peripheral or central vasoconstrictors due to synergistic elevation in blood pressure.
  - Warnings and precautions
    - Only use where a clear diagnosis of migraine has been established.
    - Co-administration with potent CYP3A4 inhibitors
    - Fibrotic complications
    - Risk of myocardial ischemia or infarction and other cardiac AEs and death have occurred. Patients with risk factors predictive of coronary artery disease (CAD) who have had a sufficient CV evaluation, should have the first dose of

DHE administered in a physician's office unless they have previously received it. Long term users of DHE should have regular CV evaluations.
    - Drug associated cerebrovascular events and fatalities
    - Increases in blood pressure
    - Local irritation
  - AEs: Rhinitis, pharyngitis, nausea, vomiting, altered sense of taste, application site reaction, dizziness.
  - Key drug interactions: Vasoconstrictors, sumatriptan, beta-blockers, nicotine.

- Bupap, Tencon, Allzital (butalbital/APAP) and Fioricet, Vtol LQ (butalbital/caffeine/APAP)
  - **Boxed warning**: Hepatotoxicity with the use of APAP > 4000 mg per day, and often occurs due to more than one APAP containing product taken at a time.
  - Contraindications: Hypersensitivity to any component, patients with porphyria.
  - Warnings and precautions
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended.
    - APAP: Hypersensitivity, anaphylaxis, serious skin reactions
  - AEs (most common): Drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.
  - Drug interactions: Alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.

- Fiorinal (butalbital/caffeine/ASA)
  - Contraindications
    - Hypersensitivity or intolerance to ASA, caffeine, or butalbital.
    - Patients with a hemorrhagic diathesis (eg, hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).
    - Patients with nasal polyps, angioedema and bronchospastic reactivity to ASA or other NSAID.
    - Peptic ulcer or other serious gastrointestinal lesions.
    - Patients with porphyria.
  - Warnings and precautions
    - ASA component: Anaphylaxis, bleeding risk
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended
  - AEs (most common): Drowsiness, dizziness

- Reyvow (lasmiditan)
  - Contraindications: None
  - Warnings and precautions: Driving impairment, CNS depression particularly in combination with alcohol or other CNS depressants, serotonin syndrome, medication overuse headache that may require detoxification.
  - AE (most common): Dizziness, fatigue, paresthesia, and sedation.
  - Key drug interactions
    - Heart lowering drugs: Reyvow may further lower heart rate when used concomitantly
    - Avoid concomitant use with P-glycoprotein and breast cancer resistant protein substrates.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cafergot (ergotamine/ caffeine)	Tablets	Oral	Two tablets at start of attack; 1 additional tablet	Maximum 6 tablets per attack or 10 tablets per week.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			every 30 minutes if needed.	Dose should start at the first sign of an attack.
Migergot (ergotamine/ caffeine) rectal suppository	Suppository	Rectal	One suppository at the start of attack; second suppository after 1 hour if needed for full relief.	Maximum 2 suppositories per attack, 5 suppositories per week. Should not be used for chronic daily administration.
Ergomar (ergotamine tartrate)	Sublingual tablets	Oral	One tablet at the start of an attack; 1 additional tablet every 30 minutes.	Maximum 5 tablets per attack or 10 tablets per week.
Migranal (dihydroergotamine mesylate)	Nasal solution	Nasal	Four sprays; 1 spray in each nostril; 1 additional spray in each nostril after 15 minutes	Maximum 3 mg in 24 hours and 4 mg in 7 days. Prior to use, the spray should be primed with 4 pumps. The applicator should be discarded with any remaining drug after 8 hours. Should not be used for chronic daily administration.
Bupap, Tencon, Allzital (butalbital/APAP)	Tablet, capsule	Oral	One to two tablets or capsules every 4 hours.	Maximum 6 tablets or capsule
Fioricet, Vtol LQ (butalbital/caffeine/APAP)	Capsule, oral solution	Oral	Capsule: 1 or 2 two tablets every 4 hours. Oral solution: 1 or 2 tablespoons (15 or 30 mL) every 4 hours	Capsule: Maximum 6 tablets Oral solution: Maximum 6 tablespoons.
Fiorinal (butalbital/caffeine/ASA)	Tablet	Oral	One to two tablets every 4 hours.	Maximum 6 tablets.
Reyvow (lasmiditan)	Tablet	Oral	One tablet (50 mg, 100 mg, or 200 mg), as needed.	Maximum 1 tablet every 24 hours. Maximum 4 tablets in 30 days. Should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery. A second dose has not been shown to be effective for the same migraine attack.

Abbreviations: APAP = acetaminophen, ASA = aspirin

- Ergotamine tartrate
  - Should only be used for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties.
  - Should not be used for daily, chronic administration.
  - Overdosage
    - Patients should be advised to report any of the following immediately: numbness or tingling in the fingers or toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, vomiting, cyanosis of the extremities.

- Fiorinal, Fioricet (butalbital component)
  - May impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery
  - Concomitant use of alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.
  - Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.
  - Acute barbiturate poisoning causing drowsiness, confusion, and coma, respiratory depression, hypotension, hypovolemic shock.

- Reyvow
  - .Drug abuse and dependence: lasmitidan is a schedule V controlled substance; Phase 2 and 3 studies have demonstrated the potential to produce euphoria or hallucinations at therapeutic doses (about 1% of patients). Patients should be evaluated/observed for risk of drug abuse/misuse.

- See the current prescribing information for full details

CONCLUSION

- Ergot alkaloids, butalbital combinations and lasmiditan are 3 classes of analgesics commonly used to treat primary headache types including migraine and TTH. Use with ergot alkaloids and butalbital combinations should be limited to treating 2 to 3 headache days a week in order to minimize the risk of MOH.
- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies. Ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism but may be enhanced with caffeine. DHE nasal spray administration bypasses this and can deliver adequate plasma concentrations for effective treatment. For moderate to severe attacks, AHS guidelines recommend the use of non-oral formulations such as DHE IN if severe nausea or vomiting are associated with a migraine attack.
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, NSAIDs, APAP), and moderate to severe attacks are treated more migraine specific agents.
- Butalbital combinations are FDA-approved for muscular headache or TTH and use has been studied in adults and pediatric patients aged ≥ 12 years. All butalbital-containing agents are paired with APAP or ASA with or without caffeine. NSAIDs and ASA are widely prescribed as acute medications for migraine. NSAIDs are still the mainstay for acute TTH, because they are less likely to lead to MOH compared to butalbital or APAP. The use of butalbital for patients with TTH may be considered in situations where NSAIDs are relatively contraindicated (eg, late in pregnancy) or when simple analgesics with caffeine are ineffective. Combination agents of butalbital with APAP may be used when other analgesics are contraindicated due to ulcers or severe renal failure. Butalbital with ASA may be used in hepatic failure.
  - The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, ASA) followed by combination analgesics containing caffeine plus a simple analgesic. Guidelines for the treatment of TTH recommends against the use of combination products with codeine or butalbital due to the increased risk of developing MOH.
- The ergot alkaloids include formulations of ergotamine tartrate (available orally and rectally) and DHE (available intranasally and as injectable forms). With the advent of triptans, the use of oral ergot alkaloids have been largely displaced in migraine therapy, as they have been found to be less effective than triptans in head-to-head trials and often reported to have poor tolerability with nausea frequently reported. The ergot alkaloids are associated with increased risk

of vascular events, so use in patients with peripheral vascular disease, coronary heart disease, or other certain CV indications are contraindicated.

- Lasmiditan is a first-in class selective 5HT-1F receptor agonist that has demonstrated efficacy in achieving pain freedom and MBS freedom 2 hours after treatment in clinical trials. According to guidelines from the AHS, lasmiditan may play a role in patients who have failed, have contraindications to, or who cannot tolerate triptans.
  - Lasmiditan is associated with driving impairment, and an inability to self-assess the degree of impairment, which is a limitation to use. Patients should be advised not to operate a vehicle (or other machinery) for at least 8 hours after administration. Common AEs include dizziness, fatigue, paresthesia, and sedation.
- Guidelines for acute migraine recommend lasmiditan as a specific therapy option on par with the CGRP inhibitors; however, safety issues may limit use. Ergot alkaloids have smaller place-in-therapy and based on efficacy and safety outcomes, European guidelines recommend avoiding ergotamine's, while US and Canada guidelines cite it as an option for acute migraine use.

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