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Pharmacokinetic and pharmacodynamic considerations with psychiatric disorders and migraines

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Case

Mr. B, age 44, presents to the clinic with increased anxiety and difficult-to-treat recurrent migraine headaches. His history is significant for migraines without aura, generalized anxiety disorder, major depressive disorder, and chronic insomnia. His current medications include aripiprazole 10 mg by mouth daily, propranolol 10 mg by mouth 3 times daily, mirtazapine 15 mg by mouth at bedtime, eletriptan 20 mg by mouth as needed for migraine, clonazepam 0.5 mg by mouth twice daily as needed for anxiety, and erenumab-aooe 70 mg subcutaneously monthly started several months ago. He has tried to identify and avoid migraine triggers with little success, and eletriptan has been minimally effective in ending migraine attacks. Since starting erenumab, he has experienced a modest reduction in frequency but still experiences multiple migraines monthly. He is looking for new options but is concerned about how his medications will "mix."

Migraine is a common and potentially disabling neurological disorder that affects an estimated 57 million people in the United States.[1] Both migraine and psychiatric disorders have some genetic inheritance associated and also can be triggered by a variety of factors, including inflammation, environment, sleep disturbances, and stress. Individuals with migraines are 2 to 4 times more likely to have symptoms of depression compared with patients without. Anxiety disorders also commonly coincide with migraines.[2] A 2021 meta-analysis of 6 studies looking at the comorbidity of anxiety and migraines reported an average odds ratio of 2.33, indicating an elevated risk of having a comorbid anxiety disorder.[3] There is a reported mean prevalence rate of 30.7% for migraine headache in patients with bipolar disorder and mean prevalence rate of 5.9% to 9% for bipolar disorder in patients who experience migraines.[4] Given the significant prevalence of psychiatric disorders with migraines, clinicians should be familiar with pharmacokinetic and pharmacodynamic considerations.

Pharmacological interventions for migraine may include acute treatments; preventative treatments; or a combination of agents based on frequency of attacks, severity of the migraine, and/or patient preference. When considering potential interactions and risk versus benefit, it is important to obtain a full medication history, review chronic and as-needed medication use, and consider the effect on mental health and quality of life.[5]

Acute Treatments

Nonopioid analgesics, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and combination products with caffeine, are appropriate first-line options for mild-to-moderate episodic migraine.[5,6] Although many of these agents are available over the counter, there are potential risks. With NSAIDs, there is an increased risk of bleeding when combined with serotonin reuptake inhibiting antidepressants, such as serotonin selective reuptake inhibitors. Patients should be counseled on these risks.[7] Those prescribed lithium should use NSAIDs with caution due to the risk of developing lithium toxicity, and caffeine-containing products may lower lithium concentrations.

Practice Points:

1. Migraine and mental health conditions are commonly encountered together.
2. Prescribers should be aware of potential pharmacodynamic interactions, such as heart rate changes, nausea, sedation, bleed risk, and dizziness.
3. The most common enzymes of concern in this population are CYP2D6 and CYP3A4.
4. Injectable CGRPs and onabotulinumtoxin A are the lowest risk options for drug interactions.

Triptans and lesser used ergotamines are agents appropriate for moderate-to-severe migraine attacks. They primarily interact with serotonin 5-$HT_{1B/1D/1F}$ receptors, although ergotamines also have affinity for norepinephrine and dopamine receptors. Theoretical interactions with 5-HT_1 and 5-HT_2 receptor agonism may contribute to the risk of serotonin syndrome (Table 1). Concern for increased risk of serotonin syndrome from concomitant use of triptans and serotonin reuptake inhibitors led to the Food and Drug Administration (FDA) issuing an alert in 2006.[8,9] However, more recent data demonstrate that this was based on a small number of reports; there is also inconsistency as to how the diagnosis was made in each case.[10,11] Despite calls for the alert to be removed, a warning persists within the triptan labeling.[12] Ergotamines are metabolized by the cytochrome P-450 (CYP P-450) enzyme CYP3A4; individuals prescribed carbamazepine, barbiturates, and/or St. John's Wort concomitantly may experience decreased efficacy from their acute treatment.[13] Monoamine oxidase inhibitors (MAOIs) that inhibit MAO-A may significantly decrease metabolism of rizatriptan, sumatriptan, and zolmitriptan. Due to toxicity risk, this combination should be avoided except for almotriptan.[14]

Lasmiditan is an agent that has similar activity compared with the triptans class, however, with increased affinity for the 5-HT_{1F} subtype receptor primarily located in the trigeminal nerve.[15] The FDA included a similar warning for serotonin toxicity in the labeling for lasmiditan both on its own and in combination with serotonin reuptake inhibitors.[12] Patients prescribed $5HT_{1B/1D/1F}$ agonists should be advised that the risk is very low, but they would benefit from education on potential symptoms of serotonin syndrome should it occur. In addition, lasmiditan is demonstrated to inhibit the intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) to a significant enough degree in vitro that in vivo activity is possible, and the combination of lasmiditan with P-gp/BCRP is not recommended. Despite the in vitro effects on CYP-2D6 noted, the impact of lasmiditan on in vivo CYP2D6 metabolism is not considered clinically relevant.[16] Lasmiditan has some central nervous system (CNS) depressant effects; caution should be considered with substance use disorders, medications that effect heart rate, and/or CNS depressants.

The calcitonin gene-related peptide (CGRP) antagonists rimegepant, ubrogepant, and zavegepant are additional options for moderate or severe migraine attacks or for mild-to-moderate attacks that do not respond to nonopioid analgesics.[5] Ubrogepant lacks clinically significant interaction with notable metabolic enzymes. It is a substrate of CYP3A4, P-gp, and BCRP although the clinical impact of interactions with the P-gp and BCRP systems appears minimally significant. Rimegepant is a substrate of both CYP3A4 and CYP2C9. Strong inducers of CYP3A4 may reduce the efficacy of rimegepant and

TABLE 1: Migraine acute treatment product interactions

Class	Product(s)	Pharmacokinetic Interactions	Pharmacodynamic Interactions
Nonopioid analgesics	Naproxen, ibuprofen, acetaminophen, aspirin, etc.	Decreased lithium clearance (NSAIDs)	Bleeding risk with SSRIs (NSAIDs)
Ergots	Ergotamine, dihydroergotamine	CYP3A4 major substrate	Hypertension and tachycardia with stimulants, theoretical serotonin syndrome (rare)
"Triptans" serotonin agonists	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Most minimally significant: Almotriptan CYP3A4 major substrate MAOIs: rizatriptan, sumatriptan, zolmitriptan	Theoretical serotonin syndrome risk (rare)
Selective 5-HT_{1F} agonist	Lasmiditan	Inhibits CYP2D6: minimally significant, P-gp and BCRP inhibitor	Heart rate changes, CNS depression, theoretical serotonin syndrome (rare)
CGRP antagonists: Gepants	Rimegepant, ubrogepant, zavegepant	Ubrogepant and rimegepant: CYP3A4 major substrate, P-gp and BCRP substrate Zavegepant: Minimally significant enzyme interactions	Nausea

BCRP = breast cancer resistance protein; CGRP = calcitonin gene-related peptide; CNS = central nervous system; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein; SSRI = selective serotonin reuptake inhibitors.

TABLE 2: Migraine preventative treatment product interactions

Class	Product(s)	Pharmacokinetic Interactions	Pharmacodynamic Interactions
Angiotensin II Receptor Blocker	Candesartan	Decreased lithium clearance	Hypotension
Beta blockers	Propranolol, metoprolol, timolol	CYP2D6 major substrates Propranolol major substrate CYP1A2 and P-gp substrate	Decreased heart rate, hypotension
Antiseizure medications	Valproic acid and derivatives, topiramate	Valproic acid: Minor CYP enzymes substrate, inhibits glucuronidation Topiramate weak inhibitor of CYP2C19 and weak inducer CYP3A4	Sedation, hyperammonemia
Calcitonin gene-related peptide antagonists	Atogepant, rimegepant Parenteral: Eptinezumab, erenumab, fremanezumab, galcanezumab	Rimegepant as above Parenteral agents lack clinically significant interactions	Nausea
Miscellaneous agents	Onabotulinumtoxin A	Clinical pharmacokinetic data lacking	None clinically significant

P-gp = P-glycoprotein.

ubrogepant, similar to the ergot derivatives mentioned earlier. It is recommended to avoid use with strong CYP3A4 inducers. Zevegepant is a minor substrate of CYP2D6, CYP3A4, and organic ion-transporting polypeptide (OATP) OATP1B1/1B3, making it a low risk for clinically significant interactions with medications for psychiatric disorders. Pharmacodynamically, CGRP antagonists have a notable incidence of nausea, which may compound with medications, including antidepressants and divalproex.[15]

Preventative Treatments

The American Headache Society recognizes several agents as having established efficacy in prevention of migraine.[5] Table 2 highlights considerations for preventative migraine treatments, including select antihypertensive agents, antiseizure medications, CGRPs, and onabolutinumtoxin A. Choice of preventative agent is based on patient-specific factors and clinical judgment.

Antihypertensive agents for prevention include the angiotensin II receptor blocker candesartan and several beta-blocking agents. Due to candesartan's effect on renal perfusion, lithium clearance can be significantly decreased when given together, and this often requires a reduction in lithium dose.[15] Select beta blockers, including propranolol, metoprolol, and timolol, have benefit in prevention of migraine. Common among these agents is their primary metabolic pathway through CYP2D6.[17] Strong-to-moderate inhibition of CYP2D6 occurs when coadministered with fluoxetine, paroxetine, bupropion, and duloxetine, thus increasing the potential for adverse effects. The addition of beta-blocking agents with CYP2D6 inhibitors may be done successfully with careful titration. Propranolol also undergoes side-chain oxidation through CYP1A2, which may be significantly impacted by fluvoxamine. It is important to make note of potential cumulative hypotensive effects with medications including benzodiazepines; alpha-receptor blocking antipsychotics, such as olanzapine and clozapine; and antihypertensives prazosin and clonidine.[18]

Select antiseizure medications find utility in migraine prevention as well as treatment of psychiatric disorders. Common agents for migraine prevention include topiramate and valproic acid derivatives. Topiramate has a minimal effect on the CYP450 system and low risk of interactions but may increase accumulation of ammonia and hyperammonemic encephalopathy when combined with valproate products.[19] Valproate products are known to inhibit glucuronidation, which increases exposure to lamotrigine and can increase risk of hypersensitivity reactions, including Stevens-Johnson syndrome. As antiseizure medications cause sedation and somnolence, it is also important to monitor for cumulative effects.

Certain CGRP antagonists are a preventative option. Injectable CGRPs are generally low risk for drug-drug interactions and have favorable safety profiles; eptinezumab, erenumab, fremanezumab, and galcanezumab lack significant interaction with metabolic processes except proteolysis.[20] Injectable CGRPs are unlikely to have significant pharmacodynamic considerations. Preventative and acute treatment with CRGPs together theoretically may increase adverse effects; however, small case studies suggest a favorable risk versus benefit when used in combination.[21] An additional preventative injectable, onabotulinumtoxin A, has a low risk of drug-drug interactions and is undetectable in blood following injection.[22] There is less data favoring its use in episodic migraine attacks, but due to its interaction profile, onabotulinumtoxin A may be an attractive option.[23]

Case Continued

When selecting treatment options for Mr. B's migraines, there are a number of considerations. Aripiprazole, mirtazapine, and

propranolol are major CYP2D6 substrates; an abortive or preventative medication that inhibits this pathway could lead to increased adverse effects. To minimize polypharmacy, Mr. B may benefit from optimizing erenumab and propranolol and/or switching acute agents. Onabotulinumtoxin A is low risk for significant interactions and can be considered as an alternative. Mr. B's erenumab was increased to 140 mg, and risk versus benefit of switching acute agents was discussed. It was determined that zamegepant would be an appropriate acute treatment over lasmiditan's potential interactions with propranolol and serotonergic agents although this combination could be used with monitoring. This regimen will be trialed for 3 months to determine effectiveness.

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