A narrative review of the importance of pharmacokinetics and drug–drug interactions of preventive therapies in migraine management

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Abstract

Objective: To review the pharmacokinetics of major classes of migraine preventives and the clinical implications of drug–drug interactions (DDIs) with the use of these therapies in migraine management.

Background: Preventive treatments for migraine are recommended for a large proportion of patients with frequent migraine attacks. These patients often exhibit a number of comorbidities, which may lead to the introduction of multiple concomitant therapies. Potential DDIs must be considered when using polytherapy to avoid increased risk of adverse events (AEs) or inadequate treatment of comorbid conditions.

Methods: A literature search was performed to identify pharmacokinetic properties and potential DDIs of beta-blockers, antiepileptic drugs, antidepressants, calcium channel blockers, gepants, and monoclonal antibody therapies targeting the calcitonin gene-related peptide pathway with medications that may be used for comorbid conditions.

Results: Most DDIs occur through alterations in cytochrome P450 isoenzyme activity and may be complicated by genetic polymorphism for metabolic enzymes. Additionally, drug metabolism may be altered by grapefruit juice ingestion and smoking. The use of migraine preventive therapies may exacerbate symptoms of comorbid conditions or increase the risk of AEs associated with comorbid conditions as a result of DDIs.

Conclusions: DDIs are important to consider in patients with migraine who use multiple medications. The development of migraine-specific evidence-based preventive treatments allows for tailored clinical management that reduces the risk of DDIs and associated AEs in patients with comorbidities.

Keywords: drug–drug interactions, migraine, pharmacodynamics, pharmacokinetics, polytherapy

Abbreviations: AE, adverse event; BCRP, breast cancer–resistant protein; CGRP, calcitonin gene–related peptide; CYP, cytochrome P450; DDI, drug–drug interaction; FcRn, neonatal Fc receptor; FDA, US Food and Drug Administration; GABA, gamma–aminobutyric acid; MAOI, monoamine oxidase inhibitor; MPS, mononuclear phagocyte system; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetics; RES, reticuloendothelial system; TCA, tricyclic antidepressant; SSNRI, selective serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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INTRODUCTION

Migraine is a disabling disorder requiring treatment for acute attacks and may require preventive therapy. The American Headache Society guidelines recommend preventive therapy in patients with frequent disabling migraine attacks (≥4 monthly headache days), contraindication to or overuse of acute therapies, or adverse events (AEs) in response to acute therapies. Approximately 39% of patients with migraine are candidates for preventive treatment; however, treatment of these patients is challenged by comorbid conditions, for example, asthma, cardiovascular disease, anxiety, depression, arthritis, sleep disorders, and chronic pain, which may require the introduction of additional therapies. Polytherapy may result in drug–drug interactions (DDIs) that can cause decreased effectiveness or ineffectiveness of prescribed drugs or adverse drug reactions, particularly when the prescribed drug may be an inducer or inhibitor of metabolic pathways of other drugs being taken.

To avoid increased risk of AEs or inadequate treatment of comorbid conditions when using polytherapy, DDIs should be considered when developing therapeutic regimens for the treatment of migraine. A risk of DDIs within migraine treatment exists even in the absence of comorbid conditions because patients using migraine preventive treatment may also require acute migraine medication for breakthrough headaches. Many DDIs are the result of coadministration of multiple drugs that undergo oxidative metabolism by the cytochrome P450 (CYP) enzymes, particularly the CYP3A4, CYP2D6, CYP1A2, and CYP2C isoenzymes. Clinically significant drug interactions can be predicted by the type of isoenzyme involved in metabolism. Thus, an understanding of the pharmacokinetic properties of migraine preventives is central to identifying potential interactions with drugs used for treatment of comorbid conditions. With the recent US Food and Drug Administration (FDA) approval of a new class of migraine preventive medications, the monoclonal antibody-based therapies, a review of the pharmacokinetic properties of migraine preventives and their potential drug interactions is timely. Here, we review the most frequently used pharmacologic classes of migraine preventives with established or probable efficacy in migraine prevention, including beta-blockers, antiepileptic drugs, antidepressants, calcium channel blockers, and monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway. In the interim, rimegepant has been approved for migraine prevention. Finally, we discuss the clinical implications of DDIs with the use of these therapies in migraine management.

METHODS

A literature search of the PubMed database was performed to identify articles related to pharmacokinetic properties of migraine preventive therapies including beta-blockers, antiepileptic drugs, antidepressants, calcium channel blockers, gepants, and monoclonal antibody therapies targeting the CGRP pathway. Articles related to the DDIs between these migraine preventive therapies and medications potentially used for comorbid conditions were also sought from the PubMed database. Other articles and data sources (e.g., prescribing information) not identified through the PubMed search were added as considered appropriate by the authors to ensure a comprehensive narrative review.

PHARMACOKINETIC PROPERTIES OF MIGRAINE PREVENTIVES

Absorption and distribution

Beta-blockers

Beta-blockers are commonly used to treat hypertension, cardiac arrhythmia, angina pectoris, and acute anxiety during public speaking and also show efficacy in migraine prevention. Propranolol, timolol, and metoprolol are classified as level A drugs (established as "effective" for migraine prevention), and nadolol and atenolol are classified as level B ("probably effective" for migraine prevention). Only propranolol and timolol are approved by the FDA for migraine prevention.

Propranolol, timolol, and nadolol have nonselective binding and have affinity for β-1 and β-2 receptors, whereas metoprolol and atenolol are β-1 selective. Beta-receptors are normally stimulated by catecholamines, which have effects on the central nervous system, respiratory system, sympathetic ganglia, the heart, peripheral arteries, and the kidney. Beta-blockers are competitors of catecholamines because of their similar structure.

Overall, beta-blockers display variable pharmacokinetic properties. After absorption from the gastrointestinal tract, beta-blockers reach peak plasma concentration in 1–3 h. Propranolol is extensively protein-bound (93%) compared with timolol (10%), metoprolol (12%), nadolol (25%), and atenolol (3%). This difference in protein-binding properties results in a higher propensity for propranolol to effectively displace other protein-bound drugs compared with other beta-blockers. In the plasma, beta-blockers bind albumin and α1-acid glycoprotein. The bioavailabilities of propranolol, timolol, metoprolol, nadolol, and atenolol are 30%, 50%–75%, 50%, 20%–30%, and 50%, respectively. Propranolol has a lower bioavailability owing to a high first-pass elimination effect. Beta-blockers have a large volume of distribution, ranging from 0.7 to 5.6 L/kg, which can be indicative of physicochemical properties (i.e., lipophilicity or hydrophilicity), can affect the duration of β-receptor blockade, as well as affect tissue concentration through extravascular penetration and diffusion through biologic barriers, such as the blood–brain barrier. More specifically, the large distribution volume of beta-blockers is indicative of their lipophilic nature, which allows them to penetrate tissues more readily and have longer duration of action compared with molecules with a lower distribution volume, depending on their target. Beta-blockers can be found in brain tissue, despite potentially low
cerebrospinal fluid concentrations, indicating that beta-blockers cross the blood–brain barrier.\textsuperscript{15} Atenolol, metoprolol, and propranolol are found in very low concentrations in breast milk. Nadolol is secreted to a greater extent, and is therefore contraindicated for use during lactation.\textsuperscript{16}

**Antiepileptic drugs**

Divalproex sodium (valproic acid/sodium valproate) is an antiepileptic drug that has FDA approval for migraine prevention and level A evidence of efficacy.\textsuperscript{9} Divalproex sodium is a teratogen and should not be used during or in anticipation of pregnancy.\textsuperscript{17} It is found in breast milk at low concentrations.\textsuperscript{16} Divalproex sodium is also used to treat manic episodes related to bipolar disorder.\textsuperscript{18}

Divalproex sodium is an antagonist of voltage-dependent Na\textsuperscript{+} channels and reduces excitatory transmission by increasing brain gamma-aminobutyric acid (GABA) concentrations.\textsuperscript{19} Divalproex sodium dissociates to valproate in the gastrointestinal tract. In the plasma, protein binding is dependent on concentration and ranges from 10\% to 18.5\%. There are three formulations for divalproex sodium, namely immediate release, extended release, and delayed release.\textsuperscript{18,20,21} The bioavailability of the extended-release formulation is 90\%, and peak plasma concentration is reached in 4–17 h.\textsuperscript{21} The volume of distribution for total valproate is relatively low at 11 L/1.73 m\textsuperscript{2}.\textsuperscript{21}

Topiramate is another antiepileptic that is approved for migraine prevention with level A evidence of efficacy.\textsuperscript{9,19} Like divalproex, topiramate is a teratogen and should be avoided during pregnancy.\textsuperscript{22} Topiramate is also found in breast milk at significant concentrations.\textsuperscript{16} Topiramate has multiple targets, such as voltage-activated Na\textsuperscript{+} channels, high-voltage-activated Ca\textsuperscript{2+} channels, GABA\textsubscript{A} receptor, AMPA/kainate receptor, and carbonic anhydrase, while it also increases GABA concentrations in the brain.\textsuperscript{23,24} It is available in immediate- and extended-release forms,\textsuperscript{25,26} has high bioavailability (>80\%), and reaches peak plasma concentrations 3.5 h after a 400-mg dose.\textsuperscript{27,28} Topiramate has a large volume of distribution (0.6–0.8 L/kg) and low plasma protein binding and is unlikely to displace protein-bound drugs.\textsuperscript{28} Topiramate is found in cerebrospinal fluid, at concentrations that correlate with plasma levels, and is assumed to cross the blood–brain barrier via nonsaturable carriers.\textsuperscript{29}

**Antidepressants**

Tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors also called selective serotonin–norepinephrine reuptake inhibitors (SSNRIs) are two classes of antidepressants used for migraine prevention. TCAs and SSNRIs are thought to prevent migraine by inhibiting serotonin and norepinephrine reuptake and maintaining serotonin levels.

Amitriptyline, a TCA with level B evidence of efficacy in migraine prevention,\textsuperscript{9} is absorbed following oral administration and reaches peak plasma concentration in 4–8 h.\textsuperscript{30} The bioavailability of amitriptyline is 32\%–62\%.\textsuperscript{31} Amitriptyline has a large volume of distribution and is widely bound to tissue and plasma proteins.\textsuperscript{32} Nortriptyline, a metabolite of amitriptyline, inhibits norepinephrine more potently than serotonin\textsuperscript{33,34} and can be used as a migraine preventive if amitriptyline is not tolerated.\textsuperscript{35}

Venlafaxine, an SSNRIs with level B evidence of efficacy, is absorbed through the gastrointestinal tract following oral administration with a peak plasma concentration reached 2 h after administration in healthy patients.\textsuperscript{9,36} Similar to amitriptyline, venlafaxine has a large volume of distribution; however, venlafaxine has low plasma protein binding and extensive tissue binding.\textsuperscript{36} Finally, amitriptyline shows low excretion levels in breast milk.\textsuperscript{16} Neither amitriptyline nor venlafaxine is FDA approved for migraine prevention.

**Calcium channel blockers**

Calcium channel blockers are commonly used antihypertensive drugs that act by blocking calcium flow through calcium channels. Several calcium channel blockers are considered effective for migraine prevention, including verapamil and amlodipine, although no calcium channel blockers are currently FDA approved for migraine prevention.\textsuperscript{37,38}

Verapamil is rapidly absorbed following oral administration, with mean peak plasma concentration reached in 2 h.\textsuperscript{39} The bioavailability of orally administered verapamil is only 10\%–20\%, due to extensive first-pass hepatic elimination.\textsuperscript{39} However, a sustained-release verapamil formulation has been found to have a relative bioavailability of almost 98\%.\textsuperscript{39} Verapamil is highly protein-bound (90\%).\textsuperscript{39} Very low levels of verapamil have been reported in breast milk.\textsuperscript{16} Amlodipine can be administered intravenously or orally.\textsuperscript{40} It is 97\% protein-bound and has an oral bioavailability of 52\%–88\%.\textsuperscript{40}

**Gepants**

Gepants are a class of CGRP receptor antagonists that are being developed for migraine treatment and prevention.\textsuperscript{41} Generally, CGRP receptor antagonists do not cross the blood–brain barrier and are not found in brain tissue.\textsuperscript{42} Rimegepant and ubrogepant are approved by the FDA for the acute treatment of migraine with or without aura in adults.\textsuperscript{43,44} Although no FDA-approved gepants are indicated for migraine prevention,\textsuperscript{43,44} rimegepant is currently under study as a dual-action acute and preventive medication for migraine.\textsuperscript{41} Furthermore, atogepant is a new gepant being developed exclusively for migraine prevention, which recently showed promising efficacy and safety results in a phase 2b/3 trial.\textsuperscript{45} Ubrogepant is administered orally, reaches peak plasma concentrations at approximately 1.5 h, and is highly protein-bound (87\%).\textsuperscript{43} Rimegepant is taken orally and reaches its maximum plasma concentration at 1.5 h.\textsuperscript{44} The bioavailability of orally administered rimegepant is approximately 64\%.\textsuperscript{44} Protein binding is approximately 96\%.\textsuperscript{44}
Monoclonal antibody therapies

Monoclonal antibody-based therapies targeting the CGRP pathway are an emerging class of migraine preventive therapies. FDA approval was first granted to erenumab in 2018, followed by fremanezumab and galcanezumab in the same year, and eptinezumab in 2020. These therapies target the CGRP receptor (erenumab or ligand [galcanezumab, fremanezumab, eptinezumab]). Therapeutic monoclonal antibodies are administered parenterally via intravenous (epineuzumab), or subcutaneous injection (erenumab, galcanezumab, and fremanezumab), due to their large size and hydrophilicity. Administration via the subcutaneous route results in lower concentrations compared with intravenous administration due to absorption via the lymphatic system. Absorption through the lymphatic system results in a longer time to reach peak plasma concentration after administration. The bioavailability of monoclonal antibodies administered subcutaneously ranges from 50% to 100%. More specifically, it is 82% for erenumab and 66% for fremanezumab. Due to their size and polarity, monoclonal antibodies are transported into tissues primarily by convective transport. Determining the volume of distribution is more complex for monoclonal antibodies compared with small-molecule drugs because elimination occurs at tissue sites that are not in rapid equilibrium with plasma. High-affinity binding and target-mediated elimination contribute to underestimation of the volume of distribution determined by noncompartmental analysis. The volume of distribution reported for the anti-CGRP monoclonal antibodies discussed here ranges from 3.7 to 7.3 L. Anti-CGRP antibodies are large molecules and do not readily cross the blood–brain barrier.

Metabolism and excretion

Beta-blockers

Most beta-blockers are eliminated by hepatic metabolism or renal excretion of the unmetabolized drug (Table 1). In general, lipophilic beta-blockers (i.e., propranolol) are eliminated mostly by metabolism, and hydrophilic beta-blockers (i.e., atenolol and nadolol) are not metabolized and primarily excreted in urine as unchanged drug. Propranolol is metabolized through glucuronidation, ring hydroxylation, and side chain oxidation by the CYP1A2, CYP2D6, and CYP2C19 isoenzymes before excretion in urine. Timolol and metoprolol are primarily metabolized by the CYP2D6 isoenzyme. Nadolol has a longer half-life compared with the other beta-blockers used for migraine prevention (14–24 h vs. 3–9 h).

Antiepileptic drugs

Divalproex sodium is primarily eliminated through hepatic metabolism via glucuronidation (30%-50%), beta-oxidation (>40%), and CYP oxidation, and only a minor fraction is excreted by the kidneys (<3%). CYP metabolism accounts for a minor fraction of the total metabolism of divalproex sodium and is mediated by CYP2C9, CYP2A6, and CYP2B6. The average half-life of divalproex sodium is 12 h (range, 8–20 h).

Topiramate is excreted predominantly unmetabolized by the kidneys and displays linear elimination kinetics. Approximately 20% of oral topiramate is metabolized in the liver by hydroxylation, hydrolysis, and glucuronidation, and its half-life is approximately 21 h (31 h for the extended-release preparation). Although its metabolism does not occur through CYP pathways, topiramate is a weak inhibitor of CYP2C19 and a weak inducer of CYP3A4.

Antidepressants

TCAs are metabolized mainly by CYP450 isoenzymes (CYP1A2, CYP2C19, CYP3A4, and CYP2D6) and excreted in urine. Amitriptyline is metabolized by CYP2C19 to nortriptyline, which is further metabolized to 10-hydroxynortriptyline and then to 10-hydroxy amitriptyline by CYP2D6. The half-life of amitriptyline is 10–28 h (16–80 h for its active metabolite nortriptyline), and one third to one half of amitriptyline is excreted within 24 h.

Venlafaxine is metabolized in the liver to the active metabolite O-demethylvenlafaxine and two minor metabolites by CYP2D6. Clearance of venlafaxine is primarily renal, and the elimination half-life is approximately 4 h for venlafaxine and approximately 10 h for O-demethylvenlafaxine.

Calcium channel blockers

Verapamil is mainly metabolized by the liver, primarily via the N-dealkylation and O-demethylation pathways. The dealkylated products, norverapamil and desalkyverapamil, are metabolized to R- and S-verapamil by CYP3A4 and CYP3A5. The elimination half-life for verapamil is 2.7–4.8 h.

Amlodipine is cleared by the liver via dehydrogenation of its dihydropyridine moiety to a pyridine derivative. It has been suggested that CYP3A4 plays a key role in the metabolic clearance of amlodipine. Amlodipine has a slow elimination half-life of approximately 34 h.

Gepants

Ubrogepant is mainly metabolized in the liver by CYP3A4 and P-glycoprotein, resulting in two glucuronide conjugate metabolites. The half-life of ubrogepant is approximately 5–7 h, and it is cleared primarily via the biliary/fecal route. Rimegepant is also primarily metabolized in the liver by CYP3A4 and to a lesser extent by CYP2C9, without any major metabolites in the plasma. The elimination half-life of rimegepant is approximately
| Therapy | Metabolism | Other metabolic pathways | Common DDIs | PK effect on |
|---------|------------|--------------------------|-------------|-------------|
| Beta-blockers | CYP1A2 | N-dealkylation glucuronidation<sup>11</sup> | Antiarrhythmics | ↑ |
| Propranolol | CYP2D6 | | Propafenone | ↑ |
| | CYP2C19<sup>11</sup> | | Quinidine | ↑ |
| | | | Lidocaine | ↑ |
| | | Calcium channel blockers | | |
| | | Nisoldipine | ↑ |
| | | Nicardipine | ↑ |
| | | Nifedipine | ↑ |
| | Other migraine medications | | | |
| | Zolmitriptan | | ↑ |
| | Rizatriptan | | ↑ |
| | Benzo diazepines | | | |
| | Diazepam | | ↑ |
| | Neuroleptic medications | | | |
| | Thioridazine | | ↑ |
| | Mesoridazine | | ↑ |
| | Chlorpromazine | | ↑ |
| | Anti-ulcer medications | | | |
| | Cimetidine | | ↑ |
| | Aluminum hydroxide gel | | ↓ |
| | Lipid-lowering medications | | | |
| | Cholestryramine | | ↓ |
| | Colestipol | | ↓ |
| | Lovastatin | | ↓ |
| | Pravastatin | | ↓ |
| | Other | | | |
| | Theophylline | | ↑ |
| | Warfarin<sup>11</sup> | | ↑ |
| Timolol | CYP2D6<sup>57</sup> | | Other beta-blockers | |
| | | | Calcium channel blockers | |
| | | | Catecholamine-depleting medications | |
| | | | Digitalis glycosides | |
| | | | Quinidine | |
| | | | Clonidine<sup>110</sup> | |
| Metoprolol | CYP2D6<sup>54</sup> | | Catecholamine-depleting medications | |
| | | | Digitalis glycosides | |
| | | | Other beta-blockers | |
| | | | Some inhalation anesthetics | |
| | | | Antidepressants | |
| | | | Fluoxetine | ↑ |
| | | | Paroxetine | ↑ |
### TABLE 1—Continued

| Therapy | Metabolism | Other metabolic pathways | Common DDIs | PK effect on PKA effect on PKA effect on PKA effect on |
|---------|------------|--------------------------|-------------|----------------|
|         | CYP isoenzyme(s) involved | | | Therapy Other drug |
| Bupropion | ↑ | | | |
| Antipsychotics | ↑ | | | |
| Thioridazine | ↑ | | | |
| Antiarrhythmics | ↑ | | | |
| Quinidine | ↑ | | | |
| Propafenone | ↑ | | | |
| Antiretrovirals | | | | |
| Ritonavir | ↑ | | | |
| Antihistamines | ↑ | | | |
| Diphenhydramine | ↑ | | | |
| Antimalarials | ↑ | | | |
| Hydroxychloroquine | ↑ | | | |
| Quinidine | ↑ | | | |
| Antifungals | ↑ | | | |
| Terbinafine | ↑ | | | |
| Anti-ulcer medications | ↑ | | | |
| Cimetidine | ↑ | | | |
| Nadolol | General anesthetics | | | |
| Antidiabetic medications | | | | |
| Catecholamine-depleting medications | | | | |
| Digitalis glycosides | | | | |
| Atenolol | Catecholamine-depleting medications | | | |
| Calcium channel blockers | | | | |
| Antiarrhythmics | | | | |
| Disopyramide | | | | |
| Amiodarone | | | | |
| Clonidine | | | | |
| Prostaglandin-synthase-inhibiting medications | | | | |
| Indomethacin | | | | |
| Digitalis glycosides | | | | |
| Divalproex sodium | CYP2C9 (inhibitor) | Mitochondrial β-oxidation | Antibiotics | ↓ |
| | CYP2A6 | Other oxidative mechanisms | | |
| | CYP2B6 | | Ertapenem | ↓ |
| | | | Imipenem | ↓ |
| | | | Meropenem | ↓ |
| | | | Rifampin | ↓ |
| | | | Other antiepileptic medications | ↑ |
| | | | Felbamate | | |
| | | | Carbamazepine | ↓ |
| | | | Ethosuximide | ↑ |
| | | | Lamotrigine | ↑ |
| | | | Phenobarbital | ↑ |
| Therapy          | Metabolism                                                                 | Common DDIs                                                                 | PK effect on* |
|------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------|
|                  | CYP isoenzyme(s) involved | Other metabolic pathways                                                                 |
| Topiramate       | CYP2C19 (inhibitor)         | Other antiepileptic medications                                                   |               |
|                  | CYP3A4 (inducer)           |                                                                                   |               |
|                  |                              | Phenytoin                                                                     | ↑             |
|                  |                              | Topiramate                                                                     |               |
|                  |                              | Antidepressants                                                                |               |
|                  |                              | Amitriptyline/nortriptyline                                                    | ↑             |
|                  |                              | Benzodiazepines                                                               |               |
|                  |                              | Clonazepam                                                                    | ↑             |
|                  |                              | Diazepam                                                                      |               |
|                  |                              | Antidiabetic medications                                                       |               |
|                  |                              | Tolbutamide                                                                   | ↑             |
|                  |                              | Other                                                                         |               |
|                  |                              | Aspirin                                                                       | ↑             |
|                  |                              | Anticoagulants (warfarin)                                                     | ↑             |
|                  |                              | Antivirals (zidovudine)                                                       | ↑             |
| Antidepressants  | CYP2C19                     | Antiarrhythmics                                                               |               |
| Amitriptyline    | CYP2D6                      | Quinidine                                                                     | ↑             |
|                  |                              | Propafenone                                                                   | ↑             |
|                  |                              | Flecainide                                                                    | ↑             |
|                  |                              | Anti-ulcer medications                                                        |               |
|                  |                              | Cimetidine                                                                    | ↑             |
|                  |                              | Other antidepressants                                                         |               |
|                  |                              | Fluoxetine                                                                    | ↑             |
|                  |                              | Sertraline                                                                    | ↑             |
|                  |                              | Paroxetine                                                                    | ↑             |
|                  |                              | MAOIs                                                                         | ↑             |
|                  |                              | Antihypertensive medication                                                    |               |
|                  |                              | Guanethidine                                                                  |               |
|                  |                              | Thyroid medication                                                            |               |

*Note: ↑ indicates an increase in plasma concentration, ↓ indicates a decrease in plasma concentration.
| Therapy                     | CYP isoenzyme(s) involved | Other metabolic pathways | Common DDIs                                      | PK effect on PKM |
|-----------------------------|--------------------------|--------------------------|------------------------------------------------|-----------------|
|                             |                          |                          | Barbiturates                                     |                 |
|                             |                          |                          | Disulfiram                                       |                 |
|                             |                          |                          | Ethchlorvynol                                    |                 |
|                             |                          |                          | Anticholinergic agents/sympathomimetic medications |                 |
| Venlafaxine                 | CYP2D6                   |                          | Anti-ulcer medications                           |                 |
|                             | CYP3A4<sup>6,115</sup>   |                          | Anti-psychotic medications                       |                 |
|                             |                          |                          | Haloperidol                                      | ↑               |
|                             |                          |                          | Risperidone                                      | ↑<sup>c</sup>   |
|                             |                          |                          | Anticoagulants                                    |                 |
|                             |                          |                          | NSAIDs                                           |                 |
|                             |                          |                          | Aspirin                                          |                 |
|                             |                          |                          | Warfarin                                         |                 |
|                             |                          |                          | Antifungal agents                                 |                 |
|                             |                          |                          | Ketoconazole                                     | ↑               |
|                             |                          |                          | Other antidepressants                             |                 |
|                             |                          |                          | Desipramine                                      | ↑               |
|                             |                          |                          | MAOIs                                            |                 |
|                             |                          |                          | Triptans                                         |                 |
|                             |                          |                          | SSRIs                                            |                 |
|                             |                          |                          | SSNRIs                                           |                 |
|                             |                          |                          | Tramadol                                          |                 |
|                             |                          |                          | St. John's Wort                                   |                 |
|                             |                          |                          | Methylenec blue                                   |                 |
|                             |                          |                          | Linezolid                                        |                 |
|                             |                          |                          | Beta-blockers                                    |                 |
|                             |                          |                          | Metoprolol                                       | ↑               |
|                             |                          |                          | Antivirals                                        |                 |
|                             |                          |                          | Indinavir<sup>115</sup>                           | ↓               |

**Calcium channel blockers**

| Therapy | CYP isoenzyme(s) involved | Other metabolic pathways | Common DDIs | PK effect on PKM |
|---------|---------------------------|--------------------------|-------------|-----------------|
| Verapamil | CYP3A4                    |                          | Statins     |                 |
|         | CYP3A5                    |                          | Simvastatin  | ↑               |
|         | CYP1A2                    |                          | Lovastatin   | ↑               |
|         | CYP2C<sup>63,116</sup>    |                          | Atorvastatin | ↑               |
|         |                          |                          | Beta-blockers|                 |
|         |                          |                          | Timolol      |                 |
|         |                          |                          | Metoprolol   | ↑               |
|         |                          |                          | Digitalis glycosides | ↑ |
| Therapy | Metabolism | Common DDIs | PK effect on a |
|---------|------------|-------------|---------------|
|         | CYP isoenzyme(s) involved | Other metabolic pathways | Therapy Other drug |
| Amlodipine | CYP3A4 | Other calcium channel blockers | |
|         | CYP3A5 | Diltiazem | ↑ |
|         |       | Antifungals | |
|         |       | Ketoconazole | ↑ |
|         |       | Itraconazole | ↑ |
|         |       | Antivirals | |
|         |       | Ritonavir | ↑ |
| Gepants | CYP3A4 (inhibitor of CYP2C8, CYP2C9, CYP2D6, and CYP2C19) | P-glycoprotein BCRP | Antifungals |
|         |       | Kitoconazole | ↑ |
|         |       | Itraconazole | ↑ |
|         |       | Fluconazole | ↑ |
|         |       | Antibiotics | |
|         |       | Clarithromycin | ↑ |
|         |       | Cyclosporine | ↑ |
|         |       | Ciprofloxacina | ↑ |
|         |       | Rifampin | ↓ |
|         |       | Calcium channel blockers | |
|         |       | Verapamil | ↑ |
|         |       | Antidepressants | |
|         |       | Fluvoxamine | |

TABLE 1—Continued
Similarly, atogepant has an approximate half-life of 10 h.\textsuperscript{44} The longer half-life of monoclonal antibodies allows for less frequent dosing, typically from 1 to 3 months (Table 2).\textsuperscript{46}

### Monoclonal antibody therapies

Monoclonal antibodies are too large to be metabolized via renal or hepatic mechanisms and are metabolized and cleared via specific target-mediated clearance and nonspecific elimination by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS).\textsuperscript{66,67} These mechanisms occur in parallel and depend on antibody concentration. Clearance rates are high at low antibody concentrations and low at high antibody concentrations, as the antigen-dependent clearance pathway is saturated and clearance occurs through the RES/MPS.\textsuperscript{66} Binding of therapeutic monoclonal antibodies to neonatal Fc receptors (FcRn) in the RES/MPS prevents clearance and contributes to the long half-life of monoclonal antibodies compared with small-molecule drugs.\textsuperscript{66} The same interaction occurs with substrates of P-glycoprotein, which is also inhibited by grapefruit juice.\textsuperscript{68} Thus, patients should be aware of the effects of grapefruit juice on migraine preventive therapies and avoid consumption.

### General metabolism considerations

The metabolism of drugs for migraine prevention raises important considerations. As mentioned previously, most preventive therapies for migraine are metabolized via CYP450 isoenzymes. Grapefruit juice can affect drug metabolism by mechanism-based inhibition of CYP450, particularly the CYP3A4 isoenzyme.\textsuperscript{68} This interaction may significantly prolong clearance of migraine therapeutics.\textsuperscript{68} The same interaction occurs with substrates of P-glycoprotein, which is also inhibited by grapefruit juice.\textsuperscript{68} Thus, patients should be aware of the effects of grapefruit juice on migraine preventive therapies and avoid consumption.
Cigarette smoking can also affect drug metabolism by CYP1A1, CYP1A2, and possibly CYP2E1, likely via polycyclic aromatic hydrocarbons found in tobacco smoke. Additionally, nicotine is metabolized in the liver by CYP2A6 and has differential effects on several CYP isoenzymes in the brain. Carbon monoxide also inhibits CYP enzymes in vitro in a dose-dependent manner. Smoking status should be assessed when deciding on migraine preventive treatments, and a smoking cessation strategy should be considered.

Genetic variations and polymorphisms in different ethnic populations should also be considered when assessing drug metabolism, although it is accepted that in this regard race is an imprecise term and can reflect heterogeneous populations. Most genes encoding CYP450 isoenzymes are highly polymorphic, with certain variants being able to alter the rate of drug metabolism in vivo. Besides CYP450, some of the most common metabolism-related polymorphisms can be found in the P-glycoprotein (ABCB1 variant) and breast cancer-resistance protein (BCRP) genes (ABCG2 variant). Additionally, P-glycoprotein expression is reduced by specific single nucleotide polymorphisms that are more prevalent in Asian and Caucasian populations.

**MIGRAINE PREVENTIVE THERAPY DDIs**

**Beta-blockers**

Propranolol, metoprolol, and timolol undergo hepatic metabolism and are, therefore, more likely to have interactions with other drugs compared with atenolol and nadolol, which are primarily excreted through the kidneys because of their relatively high hydrophilicity. Propranolol interacts with antiarrhythmic agents, calcium channel blockers, cimetidine, digoxin, ergot alkaloids, nonsteroidal anti-inflammatory drugs (NSAIDs), phenobarbital, hydrochlorothiazide, rifampin, rizatriptan, theophylline, and verapamil. Interactions with ergot alkaloids, NSAIDs, and rizatriptan are important to note, as these medications are often used in combination with migraine preventives to treat acute migraine attacks. Careful clinical monitoring is required when metoprolol is coadministered with the selective serotonin reuptake inhibitor (SSRI) paroxetine; modulation of CYP2D6 by both drugs may result in bradycardia, and dose adjustment may be necessary.

**Antiepileptic drugs**

Divalproex sodium inhibits CYP2C9 and can decrease the clearance of drugs metabolized by CYP2C9. Clearance of divalproex sodium is increased by enzyme-inducing medications, including rifampin, ritonavir, carbenoxolone, lamotrigine, phenobarbital, and phenytoin, and serum concentration is increased by aspirin, fluoxetine, felbamate, isoniazide, and chlorpromazine. Topiramate is unlikely to interact with highly protein-bound drugs and does not appear to alter the metabolism of most drugs. However, it is an inducer of CYP3A4 and inhibitor of CYP2C19 and may alter the metabolism of drugs that are substrates of these enzymes (e.g., amitriptyline, cimetidine, verapamil). Topiramate displaces valproic acid from its plasma protein-binding site; however, this interaction may not be clinically significant. Coadministration of topiramate decreases ethinyl estradiol levels, and dose adjustments at topiramate doses above 200 mg should be considered in patients using estrogen-containing contraceptives. Topiramate also interacts with metformin, which is commonly used for type 2 diabetes. This interaction leads to a decrease in metformin clearance and an increase in its maximum plasma concentration and should be taken into consideration when topiramate is considered as a migraine treatment for patients with diabetes.

**Antidepressants**

Amitriptyline and venlafaxine undergo hepatic metabolism and are subject to DDIs with drugs that share the same metabolic pathway(s). Concomitant use of TCAs with SSRIs can be considered, but may result in an increased risk of tricyclic toxicity and increased anticholinergic side effects in patients who have slow CYP2D6 metabolism and subsequent elimination of the TCA can be prolonged by the concomitant SSR1. Monoamine oxidase inhibitors (MAOIs), also used off label for migraine prevention, increase the serotonergic effect of TCAs and may cause serotonin syndrome; therefore, this combination is not advised.

Amitriptyline metabolism is decreased with coadministration of valproic acid, cimetidine, fluconazole, fluoxetine, and fluvoxamine, leading to increased risk of toxicity of amitriptyline. Coadministration of oral anticoagulants and warfarin with amitriptyline can result in decreased metabolism and possible increased antiplatelet activity. This combination is contraindicated.

**TABLE 2** PK profiles of monoclonal antibody therapies targeting the CGRP pathway

| Antibody | Time to steady state, days | Estimated half-life, days | Recommended dosing interval |
|----------|-----------------------------|--------------------------|----------------------------|
| Erenumab | ~90                         | 28                       | Monthly                    |
| Galcanezumab | Achieved after a 240-mg loading dose | 27                       | Monthly                    |
| Fremanezumab | ~168                     | ~31                      | Monthly or quarterly       |
| Eptinezumab | Achieved after the first dose | ~27                      | Quarterly                  |

Abbreviations: CGRP, calcitonin gene-related peptide; PK, pharmacokinetic.
absorption of the anticoagulants, potentially leading to increased hemorrhagic risk. Amitriptyline metabolism is increased with co-administration of carbamazepine, leading to decreased effectiveness of amitriptyline. Venlafaxine may interact with other drugs using the CYP2D6 metabolic pathway and should not be administered with MAOIs.

Calcium channel blockers

Verapamil and amlodipine undergo metabolism by CYP3A4; therefore, they are likely to have DDIs with other drugs that share the same pathway. Furthermore, both verapamil and amlodipine modulate the activity of the P-glycoprotein transporter, which affects plasma concentrations of other commonly used drugs, such as docusate and digoxin. Verapamil can cause an increased risk of severe cardiovascular depression when administered along with beta-blockers such as propranolol. Similarly, amlodipine has an increased risk of DDIs when used with atenolol or metoprolol.

Gepants

Gepants are mainly metabolized by CYP3A4 and are subject to DDIs with drugs sharing the same pathway. Furthermore, both ubrogepant and rimegepant are substrates of P-glycoprotein and BCRP; therefore, concomitant administration of P-glycoprotein/BCRP inhibitors (e.g., verapamil, itraconazole, novobiocin) may increase the exposure of these gepants. Coadministration of ubrogepant, rimegepant, or atogepant with oral contraceptives containing progestin and ethinyl estradiol did not lead to any observed increase in blood concentrations. Verapamil is a known to cause constipation by delaying colonic transit, and therefore should be used with caution in patients with constipation issues. Furthermore, there have been reports of exacerbated symptoms in patients with myasthenia gravis that followed verapamil treatment. Verapamil, in the high doses used to treat cluster headache, has also been associated with a risk of prolongation of the PR interval and atrioventricular block. As such, when verapamil is administered with other PR-prolonging medications or to those with preexisting cardiac irregularities, ECG monitoring may be warranted.

Monoclonal antibody therapies

Monoclonal antibodies are not metabolized by CYP450, so drug–monoclonal antibody interactions are not likely. A study of erenumab interaction with combined oral contraceptive (ethinyl estradiol/norgestrel) showed that there was no clinically relevant DDI. Antibody–antibody interactions are also unlikely since clearance of immunoglobulin G is dependent on saturation of FcRn, but saturation is not likely to occur at typical therapeutic doses of monoclonal antibody. No DDI information is available for mAb use with gepants.

MIGRAINE PREVENTIVE THERAPY DRUG–DISEASE CONSIDERATIONS

When assessing preventive therapies for migraine, it is important to consider their interaction with drugs used to treat other conditions. For example, the use of beta-blockers has been associated with an increased risk of cardiovascular events and a higher incidence of severe hypoglycemia among patients with diabetes mellitus. Furthermore, nonselective beta-blockers, such as nadolol or propranolol, may lead to a higher risk of severe symptom exacerbation among patients with chronic obstructive pulmonary disease. Although a large meta-analysis did not find evidence to support an increased risk of depressive symptoms in patients receiving beta-blockers, some clinicians still remain concerned about this possibility. There have also been reports of depression in elderly patients receiving lipophilic beta-blockers, which is an important consideration given the high comorbidity of migraine with depression.

When using antiepileptic drugs for migraine, it is important to consider the patient’s history with hypersensitivity to similar drugs, as some antiepileptic agents lead to high prevalence of rashes. In the case of calcium channel blockers, there are some known drug–disease interactions for verapamil that should be taken into account. Verapamil is known to cause constipation by delaying colon transit, and therefore should be used with caution in patients with constipation issues. Furthermore, there have been reports of exacerbated symptoms in patients with myasthenia gravis that followed verapamil treatment. Verapamil, in the high doses used to treat cluster headache, has also been associated with a risk of prolongation of the PR interval and atrioventricular block. As such, when verapamil is administered with other PR-prolonging medications or to those with preexisting cardiac irregularities, ECG monitoring may be warranted.

For antidepressants, caution should be exercised when administering TCAs to patients with bipolar disorder, as they are associated with an increased risk of manic or hypomanic states. In addition, venlafaxine and SSRIs are also linked to an increased incidence of mania or bipolar disorder among patients with unipolar depression. Finally, TCAs and MAOIs may exacerbate psychosis symptoms in patients with unipolar disorder with psychotic features, which does not occur with SSRI monotherapy. Besides the psychiatric risks, the cardiovascular risk of antidepressants should also be assessed. SSRIs are generally considered safe for cardiovascular complications, but patients with heart rate issues should nevertheless be closely monitored. On the other hand, SSNRIs and venlafaxine are highly associated with cardiovascular AEs. TCAs are also known for wide cardiovascular effects that can occur in patients with or without a prior history of cardiovascular disease.

Constipation-related complications have been reported with erenumab use, and patients using medication that decreases gastrointestinal motility may be at increased risk for severe constipation. The incidence of constipation AEs following long-term open-label treatment with erenumab was low, and there were no cases of treatment discontinuation due to constipation; however, patients using erenumab in a real-world setting should be closely monitored for severe constipation. Similarly, new onset hypertension or worsening of preexisting hypertension has been reported with erenumab use, most typically with single blood pressure recordings within the
first week of erenumab administration. Therefore, blood pressure should be monitored in patients receiving erenumab and considered for patients receiving other inhibitors of the CGRP pathway, despite lack of significant cardiovascular complications in short-term trials to date.

**CLINICAL IMPLICATIONS**

Despite the availability of preventive therapies for migraine, clinical management of patients with migraine is challenging when comorbidities are present. Two general approaches to treatment are treating each condition independently (polytherapy) or treating multiple conditions with a single medication (monotherapy). In the case of polytherapy, adherence is known to decrease as medication schedules become more complex. While monotherapy may have better adherence rates, it is more difficult for physicians to fine-tune dosage and administration frequency than can be done with polytherapy and may not be the optimal treatment.

When treating patients with migraine and comorbid conditions using polytherapy, the pharmacokinetic and pharmacodynamic properties of each drug must be considered. Changes in binding kinetics or rate of elimination with the introduction of additional medications may require dose adjustments and careful clinical monitoring. For example, TCAs or neuroleptics may lower the seizure threshold by blocking the GABA receptor and should be used with caution in patients with migraine and epilepsy. Furthermore, because preventive therapies are often used in tandem with acute therapies for migraine, it is especially important to consider possible DDIs when both types of therapies are prescribed simultaneously (Table 3).

Physicians should be aware of elimination pathways of drugs used for migraine prevention and possible competitive metabolic mechanisms to optimize patient care. While there are many distinct pathways and mechanisms in which DDIs can occur, most occur through alterations in CYP450 isoenzyme activity. The combination of two drugs that are substrates of, inhibit, or induce the same CYP450 isoenzyme can alter the pharmacokinetics of one or both medications, resulting in altered plasma concentrations and potential toxicity. For example, propranolol should be used with caution in patients with migraine who take cimetidine for stomach ulcers, because cimetidine reduces oxidative drug metabolism by binding to CYP450, leading to decreased propranolol metabolism and reduced systemic clearance. In addition, the propranolol–cimetidine combination has been reported to cause bradycardia.

Many DDIs can be predicted based on drug metabolism and CYP isoenzyme type, and not all DDIs are clinically significant. DDIs may become significant in patients with altered metabolism, such as patients with renal or hepatic impairment. Therapeutic monoclonal antibodies are not metabolized via CYP enzymes, and DDIs are not a major concern when incorporating monoclonal antibodies into a polytherapy regimen.

The ability to predict DDIs based on drug metabolism is complicated by genetic polymorphism for metabolic enzymes. A number of drugs are known to be affected by CYP pharmacogenetics, including propranolol and TCAs. The metabolism of propranolol is affected by genetic polymorphism for CYP1A2 and CYP2D6. For TCAs, patients who are CYP2D6 or CYP2C19 rapid metabolizers are at risk of treatment failure due to low plasma concentrations. Patients who are CYP2D6 or CYP2C19 poor metabolizers are at risk of AEs due to elevated plasma concentrations; dose adjustments or alternate therapies are recommended in these patients.

The elimination pathway of a migraine preventive drug can affect patients in other ways as well. For example, topiramate has been shown to cause type 2 renal tubular acidosis, normal anion gap metabolic acidosis, and kidney stone formation. Therefore, physicians should observe for these side effects and advise patients to be vigilant about adequate hydration.

**CONCLUSION**

Preventive treatments for migraine are recommended for a large proportion of patients with frequent migraine attacks. These patients often exhibit a number of comorbidities, which...
may lead to the introduction of multiple simultaneous therapies. Although polytherapy allows for fine-tuning of treatment regimens, DDIs are important to consider in patients taking multiple medications. The development of migraine-specific evidence-based preventive monoclonal antibody treatments allows for tailored clinical management that reduces the risk of DDIs and associated AEs in patients with comorbidities compared with therapies that have multiple mechanisms of action and/or multiple targets.

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CONFLICTS OF INTEREST

Shivang Joshi reports consulting for Allergan, Amgen, Biohaven, Lilly, Teva, and Curaxx and speaking for Allergan, Amgen, Biohaven, Lilly, and Teva. Stewart Tepper reports consulting for Aeon, Alexa, Allergan/AbbVie, Alphasights, Amgen, Aperture Venture Partners, Arazel Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CRG, Curaxx, Decision Resources, DeepBench, Eli Lilly and Company, Equinox, ExpertConnect, GLG, GSK, Guidepoint Global, Impel, M3 Global Research, Medici, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevate, Revanse, Satsuma, Slingshot Insights, Spherix Global Insights, Teva, Themania, Thought Leader Select, Trinity Partners, XOC, and Zosano; speaking and teaching for American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital (Ontario, Canada), Headache Cooperative of New England, Henry Ford Hospital (Detroit), Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians’ Education Resource, Rockpointe, ScientaCME, and WebMD/Medscape; employment with American Headache Society and Dartmouth-Hitchcock Medical Center; and other activities with Headache, Headache Currents, and Wiley Blackwell. Sylvia Lucas reports consulting or advising and/or serving on advisory committees for Allergan, Amgen, Biohaven, Impel, Lilly, Lundbeck, and Teva and consulting for Premere Blue Cross. Soeren Rasmussen and Rob Nelson are employees and stockholders of Amgen.

AUTHOR CONTRIBUTIONS

Study concept and design: Shivang Joshi, Soeren Rasmussen, Rob Nelson. Acquisition of data: Soeren Rasmussen, Rob Nelson. Analysis and interpretation of data: Shivang Joshi, Sylvia Lucas, Rob Nelson. Drafting of the manuscript: Shivang Joshi, Sylvia Lucas, Rob Nelson. Revising the manuscript for intellectual content: Shivang Joshi, Stewart J. Tepper, Sylvia Lucas, Soeren Rasmussen, Rob Nelson. Final approval of the completed manuscript: Shivang Joshi, Stewart J. Tepper, Sylvia Lucas, Soeren Rasmussen, Rob Nelson.

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