

Drug–Drug Interactions in Headache Medicine

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Background.—The main treatments in a majority of headache patients are pharmacologic therapies. As a result, it is imperative to have strong background in pharmacotherapy used to treat headaches in order to provide optimal therapy and avoid drug interactions. One of the main reasons for failure of pharmacologic treatment of headaches is drug–drug interactions (DDIs). While there are many distinct pathways and mechanisms in which DDIs can occur, most occur through alterations within the cytochrome P450 pathways (CYP). Drugs that cause induction, inhibition, or are simply substrates for these pathways are responsible for many of the DDIs.

Aim/Results.—We review and discuss the important and potential DDIs of commonly used headache medication often encountered in clinical practice. We divide the drugs into two classes, abortive and preventive. Within each group we select the most commonly used drugs and provide a detailed discussion of the mechanisms of interaction for each. Also included are commonly used herbal supplements, which can interact with headache medications.

Conclusion.—Drug–drug-interactions are a major concern when developing a treatment regimen for patients suffering from headaches. There is a growing need for physician attention to the pharmacokinetics of drugs to improve the quality of patient care. It is vital that prescribing physicians be aware of the DDIs associated with the commonly prescribed headache medications to optimize patient care and therapy results.

Key words: drug–drug interactions, cytochrome P450, headache medicine, migraine, serotonin syndrome, triptan, ergot, isometheptene, selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, antiepileptic, antidepressant, antiepileptic

Abbreviations: 5HT serotonin, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, CYP cytochrome P450, DDIs drug–drug interaction, MAO-I monoamine oxidase inhibitor, NSAIDs nonsteroidal anti-inflammatory drugs, SNRI serotonin norepinephrine reuptake inhibitor, SSRI selective serotonin reuptake inhibitor, TCA tricyclic antidepressants, SS serotonin syndrome

The mainstay treatment in headache medicine is pharmacologic therapy. As a result, it is imperative to have a strong background in headache medication pharmacotherapy, since

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Headache

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one of the major reasons for failure of headache treatment can be drug–drug interactions (DDIs).

DDIs can either cause ineffectiveness of the prescribed drug or potentiate side effects. It is not uncommon for patients to complain of side effects from a particular medication when in fact they are experiencing a DDI between their new drug and one of their previously stabilized medications.

Drug metabolism via the cytochrome P450 (CYP) system has emerged as an important determinant in the occurrence of several DDIs. A great degree of interaction predictability has been achieved through the identification of CYP isozymes and the drugs metabolized by them. There are six distinct P450 isozymes that have been identified as major drug metabolizers, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.¹

While some drugs are substrates for the CYP isozymes, others interact by increasing or decreasing CYP activity through induction or inhibition.² Medications that are CYP isozyme substrates can be metabolized through the CYP metabolic pathway. CYP isozyme inducers increase the metabolic rate of CYP isozyme activity, while inhibitors stop or diminish CYP isozyme activity. This activity is the basis behind the mechanism of how many DDIs occur and how the metabolism and clearance of other drugs can be affected. A majority of the CYP isozymes are located in the liver; however, extrahepatic metabolism can occur.³

Here, we discuss the most significant and serious interactions seen with commonly used headache medications, emphasizing the CYP system. While the majority of drugs are metabolized through the CYP isozyme systems, certain medication classes are broken down through less prominent pathways which will also briefly be discussed when reviewing them.

We will review the most significant and serious interactions seen with commonly used medications in headache medicine according to their use as abortive or preventive measures. Also, we will mention some potential DDIs that may not have been reported before, but can occur based on their pharmacology.

COMMON ABORTIVE HEADACHE MEDICATIONS

I. Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as abortive treatment for various headache types.

Important DDIs to be considered are^{4,5}:

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Conflict of Interest: None.

Diuretics

Chronic headaches, specifically certain subtypes of trigeminal autonomic cephalalgias (TACs), may require long-term NSAID use, such as indomethacin. Such patients should be educated to avoid medications which can cause volume depletion, as do *diuretics*. All medicines blocking COX-2 are potentially nephrotoxic, because they can reduce blood flow to the kidneys by preventing prostaglandin-mediated vasodilation. This is particularly true in patients who are volume depleted (dehydration), and in elderly patients.

Anticoagulants

NSAIDs should be used with caution in patients who are on anticoagulation therapy (eg, *warfarin*), due to an increased risk of bleeding. The prostaglandin inhibition property of NSAIDs can increase this risk. Patients should be properly educated and closely monitored for signs and symptoms of bleeding. Any adjustments to anticoagulation therapy need to be made in order to maintain therapeutic INR goals according to provider established INR goals of therapy.

In one study, it was shown that the risk of using NSAIDs is higher in patients who are on >40 mg/week of warfarin.⁶ Although generally the combined use of NSAIDs with anticoagulant agents is discouraged, this study was conducted on patients who were using NSAIDs daily. Since in headache medicine NSAIDs are typically used on an “as needed” basis (except in some uncommon headache disorder such as hemiparesis), there are no supporting data for recommendations on how to readjust the anticoagulant dose (specifically warfarin) in the setting of daily NSAID use.

Due to the increased risk of combining warfarin and NSAIDs in these patients, it is necessary to provide education on the risk of bleeding, and to use alternative abortive agents if possible.

Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blockers (ACE-I/ARBs)

NSAIDs promote hyperkalemia development via two mechanisms: by lowering renal renin secretion (mediated by local prostaglandin production), and by impairing angiotensin II-induced aldosterone release. A fall in aldosterone release leads to reduced potassium excretion. The concern with this class of medications is in elderly patients who are at risk of hyperkalemia. If ACE-I/ARBs are to be used in conjunction with NSAIDs, regular blood work should be performed to closely monitor potassium levels and renal function via GFR.⁷ Intervals of blood work depends on the patient's age and underlying health status.

With increased use of these classes of medications (specifically *candesartan*) in headache medicine, this possible DDI should be kept in mind.

Selective Serotonin Reuptake Inhibitors⁸

Selective serotonin reuptake inhibitors (SSRIs) can increase the antiplatelet effect of NSAIDs, which can in turn increase bleeding risk, including intracranial bleeding (*hazard ratio 1.6*).⁹ However, due to lack of high quality studies, this risk is still matter of the debate. Serotonin norepinephrine reuptake inhibitors (SNRIs) may be preferred to SSRIs when combining with daily NSAIDs.

CYP Inhibitors

Most commonly used NSAIDs for headache management (diclofenac, naproxen, and ibuprofen) are CYP2C9 substrates. Therefore, concomitant use of strong CYP2C9 inhibitors can result in increased serum concentrations of the aforementioned NSAIDs. Strong CYP2C9 inhibitors to avoid include *fluoxetine*, *paroxetine*, and the herbal supplement *gingko biloba*. Therapy modification needs to be considered in these cases. *Cranberry juice* is also a strong CYP2C9 and CYP3A inhibitor,¹⁰ and counseling to avoid or modify its consumption in patients on long-term NSAID treatment needs to be considered.

Indomethacin

Indomethacin is a commonly used NSAID in the treatment of various headaches types and is unique in that it acts as a substrate for both CYP2C9 and CYP2C19. There are two potential DDIs for consideration in this particular NSAID:

Topiramate and *valproic acid* are strong CYP2C19 inhibitors. As a result, their concomitant use with indomethacin can potentially increase gastrointestinal bleeding risk and renal toxicity of indomethacin. This is especially true for *topiramate*, which can cause metabolic acidosis and further potentiate renal failure risks. Therefore, based on current evidence, *topiramate* and *valproic acid* as preventative therapies need be reconsidered in patients requiring long-term indomethacin use.

Most of the commonly used proton pump inhibitors (*omeprazole*, *esomeprazole*, *lansoprazole*) are strong CYP2C19 inhibitors. It is common practice to place patients who are taking indomethacin daily (eg, patients with hemiparesis) on GI prophylaxis. Due to CYP interactions, the authors recommend using PPIs with weak CYP2C19 inhibitory properties (pantoprazole and rabeprazole) in order to decrease the chance of GI symptoms. This subject could be an area for future studies.

II. Triptans

MAO-Inhibitors (MAOIs)

Many triptans are metabolized via MAO-A isoenzymes. As a result MAOIs use will decrease their metabolism, resulting in high serum concentrations of triptans. Therefore, MAOIs (eg, *phenelzine*, *tranylcypromine*) should be avoided in concomitant use with triptans. Eletriptan is metabolized exclusively by

CYP3A4, and almotriptan has multiple metabolic degradation pathways, so both of these triptans are safe with MAOIs and could be used preferentially.

Ergot Derivatives

Concomitant triptan use and other vasoconstrictive agents, such as ergots (eg, dihydroergotamine, DHE), can enhance the vasoconstrictive effect of triptans and should be avoided. If patients require both a triptan and ergot, the drugs should be separated by a 24-h period.

SSRIs

Although the FDA warns about the possibility of serotonin syndrome (SS) with concomitant use of SSRIs and triptans,¹⁶ this is unlikely to be clinically significant. We discuss this in detail in the SS section below.

However, concomitant use of triptans with certain SSRIs that are strong CYP2D6 inhibitors (*fluoxetine and paroxetine*) may require a triptan dose adjustment to avoid increased triptan serum concentrations and side effects. Triptan sensations or atypical sensations are characterized by feelings of chest tightness, throat swelling, and hot flashes.

Besides generalizable class characteristics of triptans, there are drug specific features and DDIs that should be considered¹¹:

Rizatriptan

Serum concentration of rizatriptan is increased with concomitant *propranolol* use. If patients are using *propranolol*, it is best to use a different triptan other than rizatriptan or prescribe half the usual dose of rizatriptan (ie, 5 mg in adult patients). Accordingly, the maximum daily dose of rizatriptan in patients taking *propranolol* will be 20 mg instead of 30 mg.

Eletriptan

Eletriptan is a major CYP3A4 substrate. Any concomitant use of CYP3A4 inhibitors can increase the serum concentration and potential toxicity of eletriptan. Common strong CYP3A4 inhibitors to be avoided with eletriptan are *nefazodone*, some antibiotics (*clarithromycin*), most “azole” antifungal agents (*itraconazole, ketokonazole*), and *anti-retrovirals*.

Verapamil is a moderate CYP3A4 inhibitor. In patients using *verapamil*, other triptans are preferred to eletriptan.

Grapefruit juice is another CYP3A4 inhibitor. Patients taking eletriptan need to be counseled to avoid or limit this juice consumption.

In addition to the above potential DDIs, eletriptan has the highest level of protein binding among all triptans (approximately 85%). As a result, if patients are on multiple medications, it is general practice to avoid eletriptan and use alternative triptans.

Almotriptan

Almotriptan has three different routes of metabolism: MAO-A, CYP3A4, and CYP2D6. Because of the three pathways, DDIs are much less likely. The CYP2D6 almotriptan metabolism is a small percentage of the overall drug metabo-

lism (about 12%), so concomitant use of CYP2D6 inhibitors are unlikely to cause significant DDIs.

Frovatriptan

Frovatriptan is mainly metabolized by CYP1A2, and therefore use of CYP1A2 inhibitors needs to be avoided.¹² The most common potent CYP1A2 inhibitors are *verapamil, rofecoxib, fluvoxamine*, and *quinolone antibiotics*. *Peppermint and chamomile herbal teas* are potent CYP1A2 inhibitors, and patient education should be provided to avoid or limit drinking such teas while taking frovatriptan.

III. Ergot Alkaloids

This class of medication, ergotamine tartrate and dihydroergotamine mesylate (DHE), are also serotonin (5HT) agonists. In addition to action on 5HT_{1B}/5HT_{1D} (similar to triptans), they have effects on 5HT_{1A}, 5HT_{1F}, and 5HT₂. They also have activity at other receptors (*alpha-adrenergic and dopaminergic*) and comparably have more DDIs than seen with triptans. Major considerations include¹³:

Serotonin Agonists

Due to effects on 5HT_{1A} and 5HT₂ serotonin receptors, the possibility of SS with concomitant use of other serotonin reuptake inhibitors (tricyclic antidepressants [TCAs], SSRIs, and SNRIs) is a risk and combination therapy should be avoided.

Alpha 1 Agonists

Combination of DHE and this class of medication (*mido-drine*) can increase hypertensive effects and should be avoided.

Beta Blockers

Beta blockers can increase the peripheral vasoconstrictive effect of DHE, and therapy modifications may need to be considered in patients taking both.

Antibiotics/Antifungal

Certain antibiotics (*clarithromycin*) and antifungals (*ketconazole*) can increase the serum concentration of DHE, and concomitant use can intensify the adverse effects of DHE.

IV. Acetaminophen-Isometheptene-Dichloralphenazone

This combination medication is used for both migraine and tension type headaches. Isometheptene is a mild vasoconstrictor, dichloralphenazone is a mild sedative, and acetaminophen is a mild analgesic. Major DDIs occur mostly due to vasoconstrictive effects of isometheptene:

Sympathomimetic Agents

Due to the sympathomimetic activity of isometheptene, other sympathomimetics (*alpha or beta agonists*) and ergot derivatives (*DHE*) need to be avoided.

SNRIs and TCAs

SNRIs can enhance the tachycardic effect of isometheptene, and TCAs can enhance the vasopressor effect of isometheptene. Therefore, in patients who are using acetaminophen-isometheptene-dichloralphenazone as their abortive treatment

for headaches, it is better to avoid SNRIs and TCAs in their preventive regimen.

MAOIs

MAOIs enhance the adverse/toxic effect of isometheptene. Concomitant therapy should be avoided.

V. Antiemetics

Antiemetics are commonly used as migraine abortive treatments, specifically in adjunctive therapy with NSAIDs or triptans. Three major classes of antiemetics used in headache medicine are: benzamides (metoclopramide), phenothiazines (prochlorperazine, chlorpromazine, promethazine), and butyrophenones (droperidol). These three classes belong to the neuroleptic class of drugs, and all target dopamine receptors (antagonism, mainly D2). Considering that neuroleptics can prolong the QTc on cardiograms with resultant cardiac risk,¹⁴ an important DDI that needs to be considered is with other drugs which have QTc prolongation potential. These DDIs can result in serious cardiac arrhythmias (*torsades de pointes*). TCAs, SSRIs, many SNRIs, trazodone, and mirtazapine have QTc prolongation effects. Since antidepressants are also commonly used in headache medicine, DDIs with these antiemetics/neuroleptics need to be considered. This DDI is of more concern with phenothiazines and butyrophenones than benzamides.

Ondansetron, which directly works on serotonin receptors (5HT₃ antagonist) is in another class of antiemetics used in headache medicine. QTc prolongation with concomitant use of other QTc lengthening agents is still of concern with this drug. However, the FDA indicates the potential for QTc prolongation occurs in doses ≥ 32 mg.¹⁵ Since we do not use such a high dose in headache medicine, this is of less concern.

COMMON PREVENTIVE HEADACHE MEDICATIONS

I. Antidepressants

Tricyclic Antidepressants

TCAs are an old class of antidepressants widely used in headaches. They are mainly metabolized in the liver via CYP2D6, and other CYP pathways to a lesser degree. Because many medications are also metabolized through CYP pathways, there is a substantial chance for drug interactions to occur with this class.¹⁶

SSRIs/SNRIs/MAOIs

TCAs work by inhibiting serotonin and norepinephrine reuptake.

As a result, concomitant use with any other serotonin or norepinephrine reuptake inhibitor (SSRI, SNRI) are best avoided.¹⁸ MAOIs also increase the serotonergic effects of TCAs and the possibility of serotonin syndrome, thus therapy modifications need to be considered in the concomitant use of MAOI with TCAs.

Bupropion

Although bupropion is an antidepressant which does not affect serotonin reuptake, its strong CYP2D6 inhibition property results in decreased TCA metabolism. Concomitant use with TCAs may cause TCA toxicity. This combination needs to be avoided, unless there is a possibility to highly regulate and check serum concentrations of the TCA, which is often impractical.

Adrenergic Agents

The use of adrenergic medications should be undertaken with caution due to TCAs' blockade of norepinephrine reuptake. Alpha-2 agonists, such as *clonidine*, should specifically be avoided in patients taking TCAs.

Opioids

TCAs can potentiate the CNS depressant effects of other CNS depressants such as opioids. Therapy modification should be considered in this patient population. *Tramadol* is an especially dangerous opioid, since in addition to its CNS effects, its concomitant use with TCAs can increase its own *seizure* potentiating effect and also increase risk of SS.

Barbiturates

Barbiturates act in part by decreasing the firing of the locus coeruleus, a main source of norepinephrine in the brain. As a result, its use in combination with TCAs can significantly enhance the drowsiness side effect of TCAs. Barbiturates also interact with TCAs by increasing the metabolism of TCAs, consequently leading to a decreased therapeutic effect. Due to this dual effect, therapy combination of barbiturates and TCAs needs to be avoided.

Orphenadrine

Orphenadrine is a muscle relaxant that acts centrally. Providers often overlook the central depressant effects and its potential interaction with TCAs which sometime can be dangerous due to excessive sedation.

Anticholinergics

Due to the anticholinergic side effect profile of TCAs, concomitant use of other anticholinergics should be avoided (eg, *ipratropium oral inhaler*).

Diphenhydramine

Diphenhydramine is a strong CYP2D6 inhibitor, and its "regular use" in patients taking TCAs should be avoided. In addition, diphenhydramine is a potent anticholinergic.

Lithium

Lithium increases the possibility of TCA neurotoxicity, in addition to increasing SS risk and should be avoided.

St John's Wort

This herbal supplement which is used for depression, is a metabolic inducer for many CYP pathways. It can increase the metabolism of TCAs, and concomitant use is not recommended.

SSRIs

Many medications in this class are CYP inhibitors and have the potential for substantial DDIs that should be taken into consideration when prescribing. Fluoxetine and paroxetine have the highest potential to cause DDIs, since they are strong inhibitors of major CYP pathways. Citalopram and escitalopram are less potent CYP inhibitors, and thus the SSRIs of choice when patients are on multiple medications and there is a concern for interactions. However, at doses ≥ 40 mg, citalopram is a strong QTc prolonging agent, and caution is advised. Sertraline has a dose-dependent inhibitory effect. In doses < 200 mg/day, its CYP inhibitor properties are comparable to citalopram/escitalopram. Other specific DDIs to be kept in mind in this class are:

Codeine

One major notable interaction is between fluoxetine and paroxetine (and sertraline > 200 mg) with codeine. These SSRIs are strong CYP2D6 inhibitors and thus prevent the metabolic conversion of codeine to its active metabolite, morphine. Therapy modification should be considered with this drug combination, especially since this is a relatively common combination prescribed by pain specialists.

Carbamazepine

Carbamazepine is a strong CYP2C19 inducer. As a result, it increases the metabolism of SSRIs. Alternative therapy or dose adjustments should be made to account for this interaction. Carbamazepine is a CYP3A4 substrate, and the consequent CYP3A4 inhibitory action seen with fluoxetine, paroxetine, and sertraline increases serum concentrations of carbamazepine and can lead to toxicity. In certain conditions where patients may require a combination of carbamazepine and an SSRI (such as trigeminal neuralgia), it is safest to use *oxcarbazepine* (a less potent CYP2C19 inducer) and either *citalopram* or *escitalopram* (less CYP3A4 inhibitory effects).

SNRIs

This class has less potent CYP pathway inhibitory effects, and thus the occurrence of DDIs is less common when compared to SSRIs. However, due to norepinephrine reuptake inhibition, a new set of drug interactions may develop:

Adrenergic Agents

Concomitant use of an SNRI with any alpha or beta agonist medication is not recommended due to norepinephrine reuptake inhibition.

Verapamil

One important DDI is that between duloxetine and *verapamil*. Duloxetine is a CYP1A2 substrate, and *verapamil* is a strong CYP1A2 inhibitor, which can lead to higher than desired serum concentrations of duloxetine, causing increased side effects. This combination requires therapy modification.

Alcohol

Alcohol increases the potential toxicity of both SSRIs and SNRIs, and patients taking this class of medication need to be counseled to restrict alcohol.

SSRI/SNRIs and SS

SS is a potentially life-threatening condition occurring primarily due to excess stimulation of post-synaptic 5-HT_{1A} and 5HT_{2A} receptors.^{19,20}

The risk of SS is highest when SSRI/SNRIs are used with the following classes of medication:

MAOIs

This class inhibits serotonin metabolism and has a very high risk of SS.

Opioids

Some opioids, specifically *tramadol* and *meperidine*, can cause a blockade of reuptake transporters. Tramadol can act as a norepinephrine and serotonin reuptake inhibitor and also increases the release of serotonin.²¹ Therefore, we highly recommend avoiding this class of medication in patient who are on SSRI/SNRIs.

TCAs

Other classes of serotonin reuptake inhibitors such as TCAs needs to be avoided.

Lithium

Lithium increases sensitivity of post-synaptic receptors, and may induce serotonin synthesis; lithium should be avoided in patients using SSRI/SNRIs.²²

Stimulants

Amphetamine, cocaine, and 3,4-Methylenedioxymethamphetamine (Molly, MDMA) all increase release of serotonin and should be avoided.

St. John's Wort

This herbal supplement impairs reuptake of serotonin and should also be avoided. It acts as a potent inducer on many major CYP pathways. As such, it has significant interactions with most drugs used in headache medicine. Extra care should be taken to inquire if a patient is taking this supplement.

SSRI/SNRIs and Triptans

Triptans are serotonin agonists that work on the 5HT_{1B} and 5HT_{1D} receptors without significant effect on 5HT_{1A} or 5HT₂ receptors.²³⁻²⁵ Therefore, considering the pharmacology of SS detailed above, the chance of developing SS due to concomitant use of triptans and SSRI/SNRs is not higher than using SSRI/SNRIs by themselves. Recent literature suggests the risk of SS in triptan and SSRI/SNRIs use is either absent or rare; at most, the risk is uncertain.²⁶⁻²⁸ It is likely that case reports of SS occurring in the concomitant use of SSRI/SNRIs with triptans were solely due to the SSRI/SNRI agents by themselves, or the diagnosis was incorrect.

Patients taking SSRI/SNRIs should be counseled about the possibility of SS occurring regardless of being on triptans. Based on available evidence, use of triptans with SSRI/SNRIs should not be limited. It is common practice by headache experts to use the combination of SSRI/SNRIs with triptans.

II. Antiepileptics

Topiramate

Topiramate is one of the most commonly prescribed medications for headache. Although it is an effective therapeutic option, the significant side effects and drug interactions limit its use and effectiveness in practice. Topiramate is generally an overused medication in headache management, where better medications with less interactions can be used in its place. Major DDIs with topiramate include^{29,30}:

CNS Depressants

Topiramate has a significant CNS depressant effect and concomitant use of other CNS depressants can result in DDIs. Major drugs to be considered are *orphenadrine*, *hydrocodone*, and *buprenorphine*. This interaction is particularly important since many pain specialists use topiramate in addition to the aforementioned drugs. The interaction with hydrocodone is very common in clinical practice and can cause serious issues.

Carbonic Anhydrase Inhibitors

Topiramate has weak carbonic anhydrase (CA) inhibitory activity and thus its use with other CA inhibitors such as *acetazolamide* should be avoided.

Carbamazepine

Carbamazepine decreases the serum concentration of topiramate, and in patients who require combination therapy, dose adjustment need to be made.

Metformin

Topiramate increases the possibility of side effects of metformin, and alternative therapy is recommended.²⁹ If therapy modifications cannot be made, blood work should be performed routinely to monitor for metabolic acidosis. Combination therapy should be stopped immediately if metabolic acidosis is confirmed.

Oral Contraceptives

Topiramate interacts with oral contraceptives by decreasing the serum concentrations of both estrogen and progesterone, thus decreasing their effect. This effect is seen with higher dose of topiramate (>200 mg/day).³¹ Such high doses are rarely used in headache management; therefore, we are less concerned about this interaction appearing clinically in headache management. Nevertheless, all female patients of reproductive age should be counseled about using backup contraceptive methods, especially since the pregnancy risk factor of topiramate has been moved to category D.

Aripiprazole

Topiramate decreases the serum concentration of aripiprazole. In patients who are using combination therapy, the dose of aripiprazole should be adjusted.³⁰

Alcohol

Alcohol increases the serum concentration of topiramate and enhances its CNS depressant effects. This interaction is more prominent with the *extended release* forms of topiramate. Consumption of alcohol within 6 h of taking *extended-release topiramate* should be avoided.³² In general, patients taking topiramate always need to be counseled about the danger of alcohol consumption while taking this medication.

Valproate

Although DDIs are less common with valproate when compared to topiramate, its major adverse effects (hepatotoxicity, weight gain, hair loss, tremor, and potential birth defects) limit its use as headache preventive therapy. Valproic acid's therapeutic range for the treatment of epilepsy is 50–100 mcg/mL, and toxicity can occur at levels of 100–150 mcg/mL.

The major DDIs of valproate occur with other antiepileptic agents including *lamotrigine* and *carbamazepine*, which when used in combination, require dose adjustment.

- Valproic acid and its derivative products may enhance the adverse effects of lamotrigine. When valproic acid is used in combination with lamotrigine, providers should decrease the dose of lamotrigine by 50% and closely monitor patients for increased serum concentrations/toxic effects (ie, toxic epidermal necrolysis) of lamotrigine.
- Valproic acid and its derivatives may increase serum concentrations of active metabolites of carbamazepine. Additionally, the CYP induction property of carbamazepine may decrease serum concentrations of valproic acid. Carbamazepine's therapeutic range is 4–12 mcg/mL for epilepsy control. As a result, it is common practice to adjust the dose of carbamazepine as therapeutically necessary.

III. Antihypertensives

Beta Blockers

Beta blockers mainly work on peripheral receptors (beta adrenergic) and consequently have less possibility of interaction with centrally acting agents. The most important DDIs are:

Adrenergic Agents

Some antidepressants have an adrenergic blockade effect and can interact with this class. *Trazodone* has α_1 antagonistic effects, and concomitant use can cause significant orthostatic hypotension.

Ergot Derivatives

Beta blockers enhance the vasoconstrictive effects of ergots (*DHE*). In patients using *DHE* as a component of their abortive therapy, an alternative preventative medication management should be implemented.

Rizatriptan

Propranolol has a drug-specific DDI with rizatriptan (*See triptan section*). Propranolol's interaction with *zolmitriptan* is less prominent, but it is best practice to initiate *zolmitriptan* at a lower dose (2.5 mg) when patients are concomitantly taking propranolol.

Verapamil

Major drug interactions which physicians should take into consideration include:

Carbamazepine

Carbamazepine is a strong inducer of CYP1A2, and verapamil is a strong inhibitor of CYP1A2. Verapamil consequently increases the serum concentration of carbamazepine, and carbamazepine decreases the serum verapamil level. With this DDI, maintaining proper drug levels for both medications will be very difficult, and therapy modification is required.

Eletriptan

Verapamil is a CYP3A4 substrate and inhibitor, which as a result can lead to an increased serum concentration of eletriptan. For headache patients requiring the use of verapamil, a different triptan is recommended.

Oxycodone

Due to the CYP3A4 inhibitory effect, verapamil also increases the possibility of toxicity of oxycodone, and therapy modification should be considered.

ACE-I/ARBs

Major DDIs for this class are with concomitant use of NSAIDs (*See NSAID section*). Other potential DDIs are with diuretics, which can cause volume depletion (dehydration). Generally, when patients concomitantly use ACE-I/ARBs with diuretics, they need to be advised to hold off on the diuretic if they feel they are dehydrated. For example, it would advisable to avoid taking the diuretic on hot summer days or if the patient has diarrhea.

CONCLUSIONS

DDIs are a major concern when developing a treatment regimen for patients suffering from headaches. There is a growing need for physician attention to such DDIs to improve the quality of patient care. As such, medication reconciliation should be an important part of patient visits where DDIs can be identified and prevented. New changes in healthcare may require physicians to see more patients in a shorter period of time. With these changes, the necessary time allotted for medication reconciliation and review significantly decreases. Nevertheless, physicians who invest time in this vital aspect of patient care and are knowledgeable about major DDIs will have more success in treating difficult headache cases.

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