Chapter 138

Headaches in Patients with Coexisting Medical Disease

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INTRODUCTION

Headache disorders may coexist with a variety of common diseases such as hypertension, diabetes, and asthma or rare diseases such as temporal arteritis and polycythemia vera. Coexisting disorders may be the cause of the underlying headache disorder or bear no relationship to it. Their presence, however, may significantly affect the management of the underlying headache disorder. The purposes of this chapter are to (1) describe the prevalence and clinical significance of coexisting diseases within the headache patient and (2) review the use of headache medications in those with coexisting medical disorders.

PREVALENCE

Most of the large epidemiologic studies defining the prevalence of coexisting headache disorders have been conducted within cohorts of migraine patients. Diseases such as hypertension, coronary artery disease, arrhythmias, and mitral valve prolapse have a similar prevalence between migraine and nonmigraine patients. Other diseases such as cerebrovascular accidents, epilepsy, allergic diseases, asthma, depression, anxiety, panic disorder, and bipolar disorder are more common in migraine patients (14). The most prevalent diseases that coexist with migraine patients include hypertension (7 to 29%), asthma (13%), obesity (12%), and hypercholesterolemia (3 to 33%) (6,7,10).

Certain diseases may be more common in those with chronic daily headache than episodic headache disorders. Allergic disease, asthma, hypertension, and hypothyroidism were more common in those with chronic migraine when compared with episodic migraine in a study conducted in a headache-clinic population (4). The presence of obesity may also increase the likelihood of progression of episodic headache disorders to their more severe and refractory chronic forms (16). These studies could suggest that these disorders may play an important role in the "chronification" of headache disorders.

CLINICAL SIGNIFICANCE

The clinical significance of coexisting diseases depends upon their effect on the headache disorder and/or its treatment. They could affect a headache disorder in the following ways: (1) the disease or its treatment could be the cause of the headache syndrome; (2) the disease or its treatment could modulate the frequency, severity, duration, or disability of an existing headache disorder without being a causative factor; (3) the presence of the disease or its treatment could influence the choice of abortive or preventative medications in the headache patient; or (4) the use of headache medications could lead to drug interactions with those used to treat the coexisting medical disease.

DISEASES ASSOCIATED WITH HEADACHE

A number of medical diseases have been associated with the development of headache disorders and have been discussed elsewhere in this book. Medical diseases could theoretically lead to headaches through a direct or indirect effect on the trigeminal vascular pain pathways. Those diseases with a direct effect are located within the brain, meninges, dural sinuses, and intra- or extracranial arteries; most of these structures are innervated by the trigeminal nerve and pathologic processes directly activate trigeminal nociceptors. Those with an indirect effect reside distant from the head and neck and likely produce headache through their release of cytokines/hormones or

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alterations in serum oxygen saturations, electrolytes, viscosity, or hemoglobin concentrations. Others induce a secondary disease that produces headache. Examples include a hypercoagulable state leading to a thrombotic event causing headache, thrombocytopenia leading to an intracerebral hemorrhage, or a disease predisposing to intracranial hypertension.

MEDICATIONS ASSOCIATED WITH HEADACHE

A variety of medications have been associated with the development of headaches and have been discussed elsewhere. The mechanisms through which medications produce headache are not completely known. Postulated mechanisms include alterations in neurotransmitter systems (e.g., selective serotonin reuptake inhibitors, nitrates, L-DOPA, monoamine oxidase inhibitors, phenothiazines), direct neurotoxicity (e.g., cyclosporin), induction of a hypercoagulable state (e.g., estrogen, tamoxifen), potent vasoditation (e.g., nifedipine, hydralazine, minoxidil), release of cytokines (e.g., interferons, interleukin-2, monoclonal antibodies, OKT3), and production of a chemical meningitis (nonsteroidal anti-inflammatory drugs [NSAIDs], sulfa drugs).

MEDICATION USE AND COEXISTING MEDICAL DISORDERS

Medication use in the headache patient may be influenced by coexisting medical illnesses. Specific disorders such as renal or hepatic diseases may alter the metabolism or excretion of medications used to treat the headache patient. The pharmacokinetics of medications may also change in the geriatric patient. Some medications must be avoided altogether in patients with particular coexisting diseases. Beta-blockers may need to be avoided in those with asthma, and valproic acid should not be used in those with hepatic disease.

Medication use in those with coexisting medical diseases is often complicated by the potential for drug interactions. Most of the significant drug interactions involve the cytochrome (CYP) P450 metabolic pathways. Certain headache and psychiatric medications are substrates, inducers, or inhibitors of these metabolic pathways (Table 138-1). The coadministration of inducers or inhibitors of CYP pathways could alter the serum levels of substrates. An inducer would decrease serum levels of the substrate while an inhibitor would increase its levels. Headache medications that are inducers or inhibitors could pose a particular risk to patients receiving other substrate medications used to treat coexisting medical disorders. This is particularly true for medications with a narrow therapeutic index such as those used in oncologic, transplant, and human immuno deficiency (HIV) patients (discussed below). Alternatively, medications used to treat coexisting diseases that are inducers or inhibitors could alter levels of headache medications, leading to decreased efficacy or increased toxicity.

SPECIFIC DISORDERS AND POPULATIONS

Medical disorders may complicate the management of patients with headache disorders. In this section we will discuss the potential drug interactions that can occur between headache medications and those used to treat the coexisting disease. We will also review how coexisting medical disease influences our choice of headache medications.

Cancer and Chemotherapeutic Agents

There are a number of significant drug interactions between chemotherapeutic agents and headache medications. Many of the chemotherapeutic agents are substrates for cytochrome P450 pathways, and interactions typically involve these metabolic pathways. Headache medications that are inducers would lower serum concentrations of the chemotherapeutic agent, reducing their effectiveness, and inhibitors would increase levels, resulting in greater toxicity (22). Chemotherapeutic agents may also act as inducers or inhibitors for headache medications that are listed as substrates for CYP pathways (Table 138-2). Renal excretion of methotrexate may be reduced by NSAIDs, resulting in severe toxicity, and therefore this combination should be avoided (24).

Cardiovascular Diseases

Coronary artery disease can influence management of the headache patient. The triptans and ergots would be contraindicated in those with known coronary artery disease because of their propensity for mild vasoconstriction. Nonsteroidal anti-inflammatories (NSAIDs) that are nonselective cyclo-oxygenase (COX) inhibitors such as ibuprofen should be used cautiously because they could counteract the antiplatelet effects of aspirin (5). There is also evidence that some selective COX-II inhibitors may be prothrombotic, but these results remain highly controversial (11). Beta-blockers or calcium channel blockers would be a good choice for a migraine preventative because they may treat both the angina and migraine headaches.

The presence of sick sinus syndrome would lead to the avoidance of medications that depress atrioventricular nodal function (e.g., beta-blockers, some calcium channel blockers). Medications that produce arrhythmias

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TABLE 138-1 Cytochrome P450 Metabolic Pathways of Common Headache and Psychiatric Medications

Enzymes	*Substrates*	*Inducers**	*Inhibitors**
CYP 1A2	Anticonvulsants: carbamazepine Antidepressants: amitriptyline, clomipramine, imipramine, fluvoxamine, mirtazapine Antipsychotics: haloperidol, clozapine, olanzapine Triptans: frovatriptan	Carbamazepine, phenobarbital, phenytoin	Fluvoxamine
CYP 2B	Anticonvulsants: diazepam (?)	Phenobarbital, phenytoin	Fluoxetine, fluvoxamine
CYP 2C8	Anticonvulsants: carbamazepine, phenytoin	Phenobarbital	
CYP 2C9	Anticonvulsants: diazepam, phenobarbital (?), henytoin, valproic acid NSAIDs: diclofenac, ibuprofen, naproxen, piroxicam Antidepressants: amitriptyline, clomipramine, imipramine, citalopram, moclobemide Beta-blockers: propranolol	Carbamazepine (?), phenobarbital,phenytoin	Valproic acid, zonisamide Oxcarbazepine, topiramate, valproic acid (?), zonisamide (?), fluvoxamine
CYP 2E1	Anticonvulsants: phenobarbital, valproic acid	None	Zonisamide (?)
CYP 2D6	Antidepressants: amitriptyline, clomipramine, imipramine, desipramine, nortriptyline, trazodone, fluoxetine, paroxetine, citalopram, venlafaxine, mianserin, mirtazapine Antipsychotics: thioridazine, perphenazine, zuclopenthixol, haloperidol, risperidone, clozapine, olanzapine, sertindole Beta-blockers: alprenolol, Bufuralol, metoprolol, timolol, pindolol Opiates: codeine, dextromethorphan	None	Fluoxetine, paroxetine, perphenazine, thioridazine
CYP 3A4	Anticonvulsants: carbamazepine, diazepam, phenobarbital, tiagabine, zonisamide Antidepressants: amitriptyline, clomipramine, imipramine, trazodone, sertraline, nefazodone, mirtazapine Antipsychotics: haloperidol, clonazepam, risperidone, quetiapine, sertindole Ergots: dihydroergotamine, ergotamine, methergine Narcotics: methadone Triptans: eletriptan	Carbamazepine, dexamethasone, phenobarbital, phenytoin, topiramate	Cardizem, fluoxetine, fluvoxamine, verapamil, nefazodone, valproic acid (?)

Adapted with permission from (22) Vecht C, Wagner L, Wilms E. Interactions between antiepileptic and chemotherapeutic drugs. *Lancet Neurol* 2003;2:404–409; and (19) Spina E, Scordo M, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. *Fund Clin Pharm* 2003;17:517–538.
*Inducers would lower serum concentrations of the substrate medications, reducing their effectiveness, and inhibitors would increase levels, resulting in greater toxicity.
CYP, cytochrome; NSAIDs, nonsteroidal anti-inflammatory drugs.

(e.g., tricyclic antidepressants) should not be used in those with ventricular tachycardia.

Elderly Patients

The pharmacokinetics of medications differs in the elderly. Albumin levels decline with age, causing less drug to be protein bound, which may increase the free drug concentration of medications and lead to toxicity. Declines in hepatic blood flow and function of CYP enzymes with age may lead to a prolongation of elimination half-lives. Decreases in renal function may increase serum levels of drugs that are excreted by the kidneys. The elderly have an increased body fat content, and lipid-soluble drugs will have a greater volume of distribution. Therefore, lipid-soluble medications (e.g., barbiturates and benzodiazepines) have a high likelihood to cause side effects in the elderly (25).

Polypharmacy is prevalent in the elderly, increasing the likelihood of drug interactions. Many medications share the same side effects, and their concomitant use may increase the risk of an adverse event. The elderly are very sensitive to medications and should be started on the lowest possible doses of most medications to decrease the likelihood of side effects. Medications with a propensity to alter mental status (anticholinergics, benzodiazepines, antipsychotics) should be used with great caution. Tricyclic antidepressants can worsen symptoms of glaucoma and

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TABLE 138-2 Cytochrome P450 Metabolic Pathways of Chemotherapeutic Agents

Cytochrome P450 Pathway	*Substrates*	*Inducers**	*Inhibitors**
CYP 1A2	Dacarbazine, tamoxifen		
CYP 2B	Cyclophosphamide, ifosfamide, thiotepa	Cyclophosphamide, tamoxifen, dexamethasone	Thiotepa
CYP 2C8	Paclitaxel		Etoposide, teniposide
CYP 2C9			5-fluorouracil, teniposide
CYP 2C19	Nitrosoureas (?)		
CYP 2D6	Tamoxifen, nitrosoureas (?)	Tamoxifen	Doxorubicin, lomustine, vinblastine, vincristine, vindesine
CYP 2E1		Dexamethasone	
CYP 3A4	9-aminocamthotecin, cyclophosphamide, doxorubicin, docetaxel, etoposide, ifosfamide, irinotecan, nitrosoureas (?), methotrexate (?), paclitaxel, procarbazine, tamoxifen, teniposide, thiotepa, topotecan, vinblastine, vincristine, dexamethasone	Cyclophosphamide, docetaxel, paclitaxel, tamoxifen, teniposide, dexamethasone	Cisplatin (?), cyclophosphamide, doxorubicin, docetaxel, etoposide, ifosfamide, paclitaxel, teniposide, vinblastine, vindesine, dexamethasone

Adapted with permission from (22) Vecht C, Wagner L, Wilms E. Interactions between antiepileptic and chemotherapeutic drugs. *Lancet Neurol* 2003;2:404-409.
*Inducers would lower serum concentrations of the substrates, reducing their effectiveness, and inhibitors would increase levels, resulting in greater toxicity.

benign prostatic hypertrophy. Triptans and ergots can be used cautiously in the elderly, but only after a negative cardiovascular evaluation. Noncyclo-oxygenase selective NSAIDs also have a high likelihood of inducing peptic ulcer disease in the elderly.

Human Immunodeficiency Virus

Drug interactions are common in HIV patients receiving antiretroviral medications. Most of the significant drug interactions occur with the protease inhibitors. The protease inhibitors are potent CYP 3A4 inhibitors, and other medications that are substrates of this pathway should be coadministered cautiously. Eletriptan, ergot-containing medications, and calcium channel blockers should be avoided. Cases of ergotism (some fatal) have been reported with the coadministration of ergotamine and protease inhibitors (3,20). Other substrates of the CYP 3A4 pathway such as antidepressants, antipsychotics, and anticonvulsants may be used, but their doses may need to be reduced to avoid toxicity (9,22). Certain antidepressants that inhibit the CPY 3A4 enzymes may increase serum levels of protease inhibitors (e.g., fluoxetine, fluvoxamine, nefazodone) (2). Topiramate is an inducer of CYP 3A4 pathways and may decrease levels of protease inhibitors, while valproic acid is a potential inhibitor and may increase levels (22).

Drug interactions are also encountered with other antiretrovirals such as the nucleoside/nucleotide analogues, nonnucleoside reverse transcriptase inhibitors, and fusion inhibitors, but less commonly. Zidovudine levels may need be reduced in those that are given acetaminophen, indomethacin, and valproic acid. Nevirapine and other antiretrovirals (including some protease inhibitors) may decrease methadone levels in those receiving maintenance doses of this drug, leading to symptoms of acute drug withdrawal (1). There is also preliminary evidence that valproic acid could lead to increased replication of the HIV virus in vitro, and therefore this anticonvulsant should probably be avoided until this issue has been resolved (15).

Hypertension

The presence of hypertension could affect the choice of preventative medications for the migraine patient. One may choose to pick a migraine preventative that could potentially treat both disorders such as beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (17), or angiotensin II–receptor blockers (21). Some antihypertensive medications such as nifedipine and minoxidil have been associated with headaches and should probably been avoided in the headache patient.

Liver Disease

Hepatic disease could contraindicate the use of medications associated with potential hepatotoxicity. These medications include acetaminophen, trazodone, diclofenac, venlafaxine, chlorpromazine, diltiazem, acetylsalicylic acid, phenytoin, valproic acid, and carbamazepine. Acetaminophen-related hepatotoxicity is related to the dose used (>4 g/day) and more likely in those with chronic alcoholism, starvation, and concomitant treatment with phenytoin and isoniazid (12). There have been rare

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reports of topiramate leading to hepatoxicity as well (8). The authors would recommend avoidance of medications with potential hepatotoxicity in those with advanced liver disease.

Advanced hepatic disease could affect cytochrome P450 pathways, which could influence the metabolism of drugs metabolized by those pathways. For example, the cytochrome 2C19 isoenzyme is markedly reduced in those with advanced liver disease, while the 2D6 isoenzyme is less affected (12). Therefore, headache medications that are metabolized by cytochrome P450 pathways should be used cautiously or avoided in those with advanced liver disease.

Obesity

Certain preventative medications may cause weight gain and should be used cautiously in the obese patient. These include the tricyclic antidepressants, selective serotonin reuptake inhibitors, valproic acid, and gabapentin. Topiramate, however, has been demonstrated to lead to weight loss and might represent a good choice as a migraine preventative in the obese patient.

Psychiatric Diseases

Psychiatric medications are primarily metabolized by CYP enzymes and may be associated with a number of drug interactions. Fluoxetine is a potent CYP 2D6 inhibitor and may increase serum levels of drugs that are substrates for this pathway. (e.g., beta-blockers, opiates, other antidepressants, antipsychotics). Rare cases of severe bradycardia and heart block have been reported with the coadministration of fluoxetine with propranolol and metoprolol (9,23). Triptans that are metabolized by monamine oxidase enzymes should be avoided by those receiving monoamine oxidase inhibitors (e.g., sumatriptan, zolmitriptan, rizatriptan). Nefazodone is a potent CYP 3A4 inhibitor and should not be coadministered with eletriptan.

Pulmonary Diseases

Patients with a history of asthma or chronic obstructive lung disease should not be administered beta-blockers because they may exacerbate this disease. Sedative medications such as benzodiazepines may depress the respiratory drive in those with chronic respiratory failure and should be avoided.

Renal Failure and Hemodialysis

Chronic renal failure decreases glomerular filtration rates, and therefore dosage adjustments will be necessary for many medications that are excreted through the kidneys. Likewise, hemodialysis or peritoneal dialysis may decrease serum concentrations of certain medications, and sometimes supplemental dosing will be required.

Certain medications such as NSAIDs (both selective and nonselective COX) should be avoided in patients with chronic renal failure because they may lead to worsening renal failure through inhibition of renal prostaglandins. Triptans that are excreted renally (e.g., almotriptan, naratriptan, sumatriptan, rizatriptan, and zolmitriptan) should be avoided, as well as some narcotics in which toxic metabolites may accumulate (e.g., meperidine and propoxyphene) (18).

Transplantation

A number of drug interactions may result from the administration of headache medications with those used in transplant recipients. Cyclosporine, sirolimus, and tacrolimus are metabolized by CPY 3A4 enzymes and should be used cautiously with headache medications that are inhibitors and inducers of this pathway (13). Inducers may cause a decrease in serum levels of these agents, which may lead to rejection of the transplanted organ. Inhibitors could cause an increase in serum levels, leading to toxicity. NSAIDs and aspirin could decrease renal excretion of these medications, causing high serum levels of the parent compound. Valproic acid and topiramate might be avoided in liver transplant patients because of their potential for hepatotoxicity and used cautiously in other transplant patients because of their risk for drug interactions.

MANAGEMENT OF HEADACHE

Management of headache in those with coexisting medical disease depends upon the type of headache disorder. Primary headache disorders such as migraine, tension-type headache, and cluster headache are treated similarly to those without such disorders. Certain headache medications, however, may be inappropriate in those with coexisting medical illness and should be avoided or used cautiously (Table 138-3). If the headaches arise as a result of the coexisting disease, then the coexisting disease's treatment often improves the headache disorder. Headaches that occur secondary to medication use can be improved through withdrawal of the offending agent or a reduction in its dose.

CONCLUSIONS

Coexisting medical diseases commonly occur in headache patients. Such diseases and/or their treatments may be the cause of the underlying headache disorder or have no relationship to it. Even in the absence of a causal relationship they can have a profound influence on the

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TABLE 138-3 Potentially Inappropriate Use of Headache Medications in Patients With Medical Disease

Disease or Condition	*Medication**	*Concern*
Arrhythmias	TCAs	May have proarrhythmic effect and prolong QT interval
Asthma	Beta-blockers	May worsen bronchospasm
Benign prostatic hypertrophy	TCAs, muscle relaxants	Anticholinergic effect may lead to urinary retention
Blood clotting disorders or receiving anticoagulant therapy	ASA, NSAIDs, dipyridamole, ticlopidine, clopidogrel	May prolong bleeding time, elevate INR values, or inhibit platelet aggregation, resulting in increased potential for bleeding
Cancer and chemotherapeutic agents	Avoid CYP inducers, and inhibitors	May cause drug interaction with chemotherapeutic agent
Cardiac conduction disease	Verapamil, beta-blockers	May lead to high-grade atrioventricular block
Constipation	Verapamil, TCAs, anticholinergics	May worsen constipation
Coronary artery or cerebrovascular disease	Triptans, ergots	Vasoconstrictive effect may increase likelihood of ischemic event
COPD	Long-acting benzodiazepines, beta-blockers	May exacerbate or cause respiratory depression
Dementia	Barbiturates, anticholinergics, muscle relaxants, topiramate	May worsen memory impairment
Depression	Beta-blockers, benzodiazepines	May worsen depression
Gastric or duodenal ulcers	NSAIDs or ASA	May exacerbate existing ulcers or produce new ulcers
Heart failure	Calcium channel blockers	May have negative inotropic effect on heart
Hepatic diseases	Acetaminophen, trazodone, diclofenac, venlafaxine, chlorpromazine, diltiazem, asparin, phenytoin, valproic acid, carbamazepine	May worsen liver function in those with advanced liver disease
HIV	Avoid CYP 3A4 inducers or inhibitors; methadone	May cause drug interaction with antiretrovirals
Obesity	Valproic acid, olanzapine, gabapentin	May increase weight
Parkinson disease	Metoclopramide, antipsychotics	Antidopaminergic effect may worsen symptoms
Renal failure	Meperidine, NSAIDs, propoxyphene	May worsen renal failure or lead to toxicity
Seizures	Bupropion, TCAs	May lower seizure threshold
SIADH or hyponatremia	SSRIs	May cause SIADH or worsen hyponatremia
Syncope or orthostatic hypotension	Antihypertensives, TCAs	May worsen orthostatic hypotension and lead to falls
Transplantation	Avoid CYP 3A4 inducers or inhibitors	May increase or decrease cyclosporine, tacrolimus, or sirolimus levels

Adapted with permission from Fick D, Cooper J, Wade W, et al. Updating the Beers criteria for potentially inappropriate medication use in the elderly. *Arch Intern Med* 2003;163:2716–2724.
*ASA, aspirin; COPD, chronic obstructive pulmonary disease; CYP, cytochrome; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

clinical course, prognosis, and choice of medications for the headache patient. The physician must be particularly vigilant to avoid drug interactions that can occur between headache medications and those used to treat the underlying coexisting disease. Therefore, a complete knowledge of coexisting medical diseases and their treatment is necessary to provide appropriate management to the headache patient.

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