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This issue of Primary Care Reports *concludes the series on headache disorders. Part I covered headache history, physical examination, diagnostic testing, and differential. Part II addresses common headache diagnoses and their management.*

—The Editor

Common Headache Disorders: Diagnosis and Management, Part II

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Migraine

The prevalence of migraine in the United States is 20% in women and 8% in men. Aura, usually scintillating scotomata or fortification spectra, precede the headache in about 15% of patients.

Most migraines are precipitated only when several triggers occur in close temporal proximity, usually in the 12 hours preceding the migraine onset. The simultaneous elimination of multiple headache triggers has an additive effect in decreasing the probability that the migraine threshold will be crossed. Migraines are rarely induced 100% of the time upon exposure to individual triggers.

The most common migraine trigger factors are alcohol and four food substances: tyramine (found in aged cheese, fermented foods), aspartame (found in many diet soft drinks), monosodium glutamate (MSG, found in Chinese restaurant food, flavor enhancers), and phenylethylamine (found in chocolate). Additional common trigger factors are hormonal changes (menses, climacteric), alterations in sleep patterns (shift changes, jet lag, sleeping late on weekends), fasting, weather changes, and "let down" after stress (weekends, vacations).

Treatment. *Prophylactic Medications.* A wide variety of medications have been utilized in the prophylaxis of migraine, including methysergide (Sansert), beta blockers, calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, divalproex (Depakote), topiramate (Topamax), and cyproheptadine (Periactin). Methysergide is no longer used today for migraine prophylaxis due to the risk of serious complications such as retroperitoneal fibrosis. Cyproheptadine (Periactin) generally is used for migraine prophylaxis in children (off-label use). Adults often find the side effects of fatigue and weight gain

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from this antihistamine/antiserotonin drug difficult to tolerate.

Several beta blockers have been shown to be effective in migraine prophylaxis. Among these are propranolol (Inderal) and timolol (Blockadren) (the only beta blockers currently approved by the U.S. Food and Drug Administration for migraine prophylaxis), nadolol (Corgard), metoprolol (Lopressor, Toprol), and atenolol (Tenormin). Beta blockers with intrinsic sympathomimetic activity, such as pindolol (Visken) and acebutolol (Sectral), have not been found useful in migraine prophylaxis.

While generally well tolerated, beta blockers are contraindicated in patients with bronchospastic disease (i.e., asthma, emphysema, chronic bronchitis), diabetes mellitus, and Wolff-Parkinson-White syndrome. Beta blockers also may exacerbate Raynaud's phenomenon, a condition found more commonly in migraine sufferers. Side effects of beta blockers include depression, fatigue, and sleep disorders. Depression is more commonly reported with propranolol than with other beta blockers.

The antiepileptic agents divalproex (Depakote) and topiramate (Topamax) have been FDA-approved for migraine prophylaxis. Common side effects with divalproex include nausea, asthenia, somnolence, and weight gain. Potentially life-threatening adverse effects of divalproex include hepatotoxicity, pancreatitis, and teratogenicity. Common adverse effects of topiramate include cognitive dysfunction, depression, somnolence, anorexia, and weight loss.

Calcium entry blockers may be useful in the prophylaxis of migraine and cluster headache (off-label use). Several calcium entry blockers have been shown to be effective in migraine prophylaxis, including verapamil (Isoptin, Calan, Verelan), diltiazem (Cardizem), flunarizine, nimodipine (Nimotop), and nicardipine (Cardene). Nifedipine (Procardia, Adalat) is either weakly effective or ineffective for migraine prophylaxis and can exacerbate migraine in some patients because of profound vasodilation. In the United States, verapamil is considered the calcium channel blocker of choice for migraine and cluster prophylaxis (off-label use).

The calcium entry blockers constitute a diverse group of drugs with varying effects on the heart and peripheral vasculature. Verapamil and diltiazem have negative inotropic effects and slow conduction through the AV node. Therefore, these agents should be avoided in patients with congestive heart failure, advanced heart block, or sick sinus syndrome. The dihydropyradine calcium entry blockers nifedipine , nicardipine (Cardene), and nimodipine (Nimotop) have no effect on cardiac conduction but can cause marked vasodilation.

Adverse effects with calcium entry blockers include constipation with verapamil (Isoptin, Calan, Verelan); sedation, weight gain, and Parkinsonism with flunarizine; flushing and edema with nifedipine; and gastrointestinal upset and Parkinsonism with diltiazem.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are valuable in both the prophylaxis of migraine headache and as adjunctive therapy for tension-type headache (off-label use). This dual effect on migraine and tension-type headache allows for NSAIDs to be used as single-drug therapy in some patients with the mixed headache syndrome.

Several NSAIDs have been reported to have prophylactic activity in migraine (off-label use). Among these are aspirin, naproxen (Naprosyn), flurbiprofen (Ansaid), ketoprofen (Orudis), and fenoprofen (Nalfon).

Adverse effects from NSAIDs are relatively common and may include gastrointestinal symptoms such as dyspepsia, heartburn, nausea, vomiting, diarrhea, constipation, and generalized

Executive Summary

- Common prophylactic agents for migraine include beta blockers, calcium channel blockers, NSAIDs, tricyclic antidepressants, divalproex, topiramate, and cyproheptadine.
- Abortive agents for migraine include NSAIDs, triptans, and ergotamine preparations.
- Biofeedback, physical therapy, and acupuncture are the common nonpharmacologic therapies for chronic tension-type headache.
- Oxygen therapy is the accepted safest and most effective treatment for cluster headaches.
- Analgesic medication overuse occurs in more than one quarter of patients with chronic daily headaches.
- Although no drugs are approved by the FDA specifically for the treatment of chronic daily headaches, medications with central pain modulating effects tend to be the most effective modality.

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Table 1. Red Flags in the Diagnosis of Headache[55]

- Onset of headache after age 50
- Onset of new or different headache
- "Worst" headache ever experienced
- Onset of subacute headache that progressively worsens over time
- Onset of headache with exertion, sexual activity, coughing, or sneezing
- Headache associated with any of the following changes in neurological evaluation:
  - Drowsiness, confusion, memory impairment
  - Weakness, ataxia, loss of coordination
  - Numbness and/or tingling in extremities
  - Paralysis
  - Sensory loss associated with headache
  - Asymmetry of pupillary response, deep tendon reflexes, or Babinski response
  - Signs of meningeal irritation
  - Progressive visual or neurological changes
  - Other evidence to suggest an underlying neurological disorder, such as persistent tinnitus, loss of sense of smell, loss of sensation over the face, dysphagia, etc.
- Abnormal medical evaluation:
  - Fever
  - Stiff neck
  - Hypertension
  - Weight loss
  - Tender, non-pulsatile temporal arteries
  - Papilledema
  - Evidence to suggest a systemic illness

abdominal pain. Most NSAIDs can cause bleeding of the upper gastrointestinal tract. Renal effects of NSAIDs may include decreased glomerular filtration rate (GFR) with sodium, chloride, and water retention. Renal problems are most likely to occur in patients who are elderly, hypertensive, have renovascular or advanced atherosclerotic disease, or take diuretics. Indomethacin (Indocin) and fenoprofen (Nalfon) appear to be more nephrotoxic than other NSAIDs. Analgesic nephropathy, the most common cause of drug-induced renal failure, has been associated with excessive use of NSAIDs along with phenacetin or acetaminophen (Tylenol).

Abortive Medications. For the abortive (acute) treatment of migraine headaches, many guidelines suggest starting with an NSAID (off-label use). The most effective NSAIDs to abort migraine attacks are naproxen sodium, flurbiprofen, and meclofenamate. Generally, a dose is given at the onset of the headache (naproxen sodium 550 mg, flurbiprofen 100 mg, meclofenamate 200 mg) and repeated in one hour if the headache still is present. Many patients self-treat with over-the-counter NSAIDs prior to seeking medical consultation.

Patients whose migraines are associated with moderate to significant disability or whose attacks fail to respond to simple analgesics or NSAIDs may be candidates for a triptan (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, eletriptan). These "migraine-specific" therapies are structurally related to the neurotransmitter serotonin (5-hydroxytriptamine, 5-HT). They are potent and selective agonists for the 5-$HT_{1B/1D}$ receptors, which are largely restricted to blood vessels, particularly in the internal carotid and middle cerebral arteries, and the trigeminal nerve. The triptans have no known analgesic effect per se. These agents relieve not only head pain but also associated symptoms of nausea, vomiting, photophobia, and phonophobia.

While triptans are most effective when given while the migraine pain is mild, they can be effective even if given long after the onset of migraine during the peak intensity of headache. This feature makes these drugs useful for patients who frequently awaken with a fully evolved migraine. Triptans are prescribed to abort a migraine attack. If they fail to do that with one dose, or in some cases with one more dose given 2-4 hours later, it is unlikely that these medications will help this attack. Rescue medicatons to reduce pain and the migraine's accompanying symptoms then should be used. Additional doses beyond one to two should be kept in reserve only for headache recurrence (when a headache occurs within 24 hours of relief from the initial attack). In other words, triptans are never used as needed for pain. Use of these medications more than two times during a treatment day (24 hours) or more than 6-8 treatment days per month signals a need for patient re-evaluation. A triptan should not be given concurrently or within 24 hours of other triptans, related ergot-containing preparations, or ergot-like medications (dihydroergotamine) due to the potential for additive vasoconstrictor effects. Triptans may cause mild, transient elevation of blood pressure and may cause coronary vasospasm. They are contraindicated in patients with documented or suspected ischemic heart disease, history of myocardial infarction, documented silent ischemia, Prinzmetal's angina, suspected coronary heart disease, and uncontrolled hypertension. These drugs have not been studied for management of basilar or hemiplegic migraine.

Triptans may be partnered with NSAIDs either individually or in a fixed-dose combination tablet (sumitriptan plus naproxen sodium). This combination may provide a small additive effect in treating mild to moderate migraine.[1] There is no compelling reason to select the fixed-dose combination over other triptans and NSAIDs.[2]

Ergotamine tartrate usually is effective for migraine, but, because of the problem of adverse effects and ergotamine rebound with frequent use, it is used only if the other medications are ineffective. The usual oral dose is 2 mg initially, followed by 1 mg every 30 minutes, as needed, with a maximum of 6 mg daily and 10 mg per week. Rectal absorption of ergotamine is greater than oral absorption. To reduce the likelihood of nausea, a 2 mg rectal suppository should be cut into thirds, with one-third given as the initial dose and additional thirds every hour as needed, up to the maximum of 6 mg per day. When

ergotamine is prescribed, it should be given no more often than every four days to prevent medication overuse headaches.

Dihydroergotamine (DHE-45) can be given intramuscularly (1 mg), subcutaneously (1 mg), or intranasally (2 mg). Repetitive doses of intravenous dihydroergotamine (DHE-45) may be given to abort prolonged (status) migraine. Parenteral dihydroergotamine (DHE-45) usually will induce nausea; pretreatment with an anti-emetic is recommended.

Vasoconstrictors, such as ergotamine preparations, triptans, and isometheptene products, should be avoided in patients with coronary artery disease, peripheral vascular disease, or poorly controlled hypertension.

Chronic Tension-Type Headache

The tension-type headache is the most common form of headache in Western populations. Tension-type headache typically is described as a band-like pressure headache without associated symptoms. The International Headache Society[3] defines tension-type headache as a bilateral headache having a pressing or tightening quality of mild to moderate severity. Unlike migraine, it is not aggravated by physical activity, nor is it associated with vomiting. Phonophobia or photophobia may be present, but not both. In chronic tension-type headache, but not episodic tension-type headache, patients may experience nausea. By definition, chronic tension-type headache occurs at least 15 days per month for at least 6 months,[3] although in clinical practice, it usually is a daily or almost daily headache.

Previously used names for tension-type headache included muscle contraction headache, psychogenic headache, and chronic daily headache. The term "muscle contraction headache" was abandoned because electromyographic (EMG) evidence failed to show consistent changes in muscle tone in patients with tension-type headache. Further, it suggested a pathophysiologic mechanism for the headache that has yet to be proven.

The concept that tension-type headache is a "psychogenic" headache has also been questioned. Patients with chronic tension-type headache, like patients with other chronic pain disorders, have about a 25% likelihood of developing secondary depression. Half of these patients develop depression simultaneously with the pain, while in the other half, the development of depression is more insidious.[4] Tension-type headache may be present in almost all psychiatric disturbances.[5] This should not suggest, however, that most tension-type headache is associated with psychiatric or psychological disorders.

The pathophysiology of tension-type headache is poorly understood. It is probable that episodic tension-type headache is predominantly a disorder of peripheral mechanisms, while chronic tension-type headache reflects a central pain disturbance.

Treatment. Despite its frequency in the population and its societal impact, there are very few well-controlled studies of treatment of tension-type headache. Many earlier trials included patients with combined tension-type and migraine without aura and patients with medication overuse headache.

Given the chronic nature of the disorder and the risk of medication-overuse headache in patients with frequent headaches, prophylactic therapy is warranted for most patients with chronic tension-type headache.

Preventive Medications. *Tricyclic Antidepressants.* Tricyclic antidepressants are the drugs of choice for chronic tension-type headache (off-label use), and several of these agents also are effective in migraine prophylaxis (off-label use). The antidepressants that have been tested in double-blind, placebo-controlled studies of patients with chronic tension-type headache include amitriptyline, doxepin, maprotiline,[6] and nortriptyline.[7] Other tricyclic antidepressants also may be effective, although they have not been studied in this population. In children and elderly patients, the usual starting dose of amitriptyline (or a similar drug) is 10 mg at bedtime. In adults, the usual starting dose is 25 mg at bedtime. The dosage can be increased every few days until a therapeutic result is obtained or side effects become intolerable. Antidepressants usually take 4-6 weeks to show beneficial effects.

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and citalopram[8-10] have not shown efficacy in controlled studies. Since they lack efficacy in headache prophylaxis, they should be considered only for patients who cannot tolerate or who fail tricyclic therapy (off-label use).

Muscle Relaxants. Cyclobenzaprine is a muscle relaxant that is related structurally to amitriptyline. In a 1972 double-blind study,[11] 10 of 20 patients receiving cyclobenzaprine showed a 50% or greater improvement in chronic tension-type headache, whereas only 5 of 20 patients receiving placebo were improved. The usual dose of cyclopenzaprine is 10 mg at bedtime (off-label use). Tizanidine, an alpha-adrenergic blocker, was reported to be effective for chronic tension-type headache in a single placebo-controlled study.[12] The dosage was titrated from 2 mg at bedtime to 20 mg per day, divided into three doses. Sedation is the most common adverse effect of this agent (off-label use).

NSAIDs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed both as adjunctive therapy for tension-type headache and for the prophylaxis of migraine headache.[13] There are no randomized controlled trials of their efficacy in the prophylaxis of chronic tension-type headache (off-label use), but several NSAIDs have shown efficacy for migraine prophylaxis.[13]

Valproate. Valproate, a GABA agonist anticonvulsant, has been evaluated for efficacy in migraine[14,15] and "chronic daily headache"[16] and found to lead to significant improvement in many patients (off-label use for tension-type headache or chronic daily headache). Commonly reported side effects include weight gain, tremor, hair loss, and nausea. There is a significant risk of birth defects with valproate. It should not be used in women who may become pregnant.

Botulinum Toxin. Botulinum toxin A injections into the muscles of the head and neck have been studied for the relief of chronic tension-type headache and migraine. A review of the studies utilizing evidence-based medicine criteria[17] concluded that the studies did not support the prohylactic treatment of pri-

mary headaches with botulinum toxin A (off-label use).

Abortive Therapy. Treatment of the daily, tension-type headache with abortive medications is difficult. Muscle relaxants such as chlorzoxazone, orphenadrine citrate, carisoprodol, and metaxalone, either alone or in combinations with aspirin, acetaminophen, and/or caffeine, commonly are prescribed to patients with chronic tension-type headache (off-label use), but they have not been shown to be effective for acute headache relief.[18] NSAIDs may be useful as analgesics for daily headache and lack the potential for causing medication-induced headache.[19] Sumatriptan has been evaluated in several studies in tension-type headache.[20,21] The drug was no more effective than placebo in acute attacks for patients with chronic tension-type headache (off-label use); however, severe episodic tension-type headaches in patients with coexisting migraine appear to respond to this agent.[22] Benzodiazepines, butalbital combinations, and opioids should be avoided, or their use carefully controlled, because of the risk of habituation and analgesic-overuse headache with frequent use.

Non-pharmacologic Therapy. Non-pharmacologic therapy has an important role in the management of chronic headache syndromes. The most commonly used techniques are biofeedback, acupuncture, and physical therapy.

Biofeedback. Biofeedback can help patients change vasomotor tone and relax tight muscles. Biofeedback refers to a collection of techniques in which the physiologic activity of unconscious bodily functions is monitored and provided instantly by audio or visual instruments in an attempt to permit the patient to gain control over these functions. The rationale underlying biofeedback assumes that the physiologic activity being monitored is causally related to a clinical problem and that alteration of the physiologic activity can lead to resolution of that problem.

Biofeedback for tension-type headache primarily measures electromyographic (EMG) changes in the tension of the frontalis muscle or in the most tense muscle in the head or neck. The patient is instructed to use thoughts, feelings, or other strategies to reduce the muscle tension. Daily home practice of these skills is encouraged. Meta-analysis[23] of this technique showed posttreatment improvement of 61% (compared with placebo response of 35%). Relaxation training alone was statistically equivalent to biofeedback (59%), and the combination of relaxation training and EMG biofeedback was also equivalent (59%) in efficacy.

Biofeedback for migraine also may utilize EMG but usually includes thermal biofeedback. Patients are taught to increase the surface temperature of their hands, causing a reduction in sympathetic tone. The technique of thermal biofeedback is similar to EMG biofeedback. Meta-analysis of frontalis EMG biofeedback with relaxation training in migraine subjects showed posttreatment improvement of 65%, relaxation therapy showed posttreatment improvement of 53%, and thermal biofeedback showed posttreatment improvement of 52%.

Many clinical studies have supported the utility of relaxation and EMG biofeedback therapies in the management of chronic tension-type headache.[23] Averaging the results of 37 trials that used daily headache recordings to evaluate relaxation or EMG biofeedback therapies, each therapy or the combination yielded a 50% reduction in tension-type headache activity. Studies have not found differences between the efficacy of relaxation, biofeedback, or the combination. Stress management therapy utilizing cognitive-behavior therapy is as effective as relaxation or biofeedback therapy in reducing tension-type headache. Cognitive therapy may be most likely to enhance the effectiveness of relaxation or biofeedback therapies when chronic stress, depression, or adjustment problems aggravate the patient's headaches.[23]

The combination of non-pharmacologic therapy and pharmacotherapy provides greater benefit than either therapy used alone. The addition of guided imagery to pharmacologic therapy resulted in significant improvements in both health-related quality of life and headache-related disability.[24] In a placebo-controlled study comparing tricyclic antidepressant medication with stress management therapy, both modalities were modestly effective by themselves in treating chronic tension-type headache, but combined therapy was better than monotherapy.[7] Non-pharmacologic therapy is particularly useful for patients who are reluctant to take medications due to desire for pregnancy, previous adverse reactions to medications, or concomitant medical problems. While biofeedback and stress management usually require referral to psychologists, guided imagery and relaxation therapy can be learned from audio tapes available at most bookstores.[18]

Physical Therapy. Physical therapy is used to train patients to strengthen neck muscles, improve mobility, and correct poor posture. Physical therapy should not be limited to heat and massage. Although heat and massage provide short-term pain relief, only strengthening exercises provide long-term benefit.

Acupuncture. Acupuncture has been shown to be effective for the treatment of migraine and tension-type headache in a number of controlled clinical studies. Pain reduction of 31% was reported in tension-type headache. No major side effects were reported with acupuncture.[25,26]

Cluster Headache

Cluster headache is marked by cycles of headache lasting one to four months separated by remissions of six to 24 months. Ten to 20% of cluster patients suffer with chronic cluster headache, which lasts greater than one year without remission. The cluster headache attacks are always unilateral, and are located around the eye, temple, or upper jaw. Parasympathetic overactivity results in reddening and tearing of the eye, nasal stuffiness, and rhinorrhea. Partial sympathetic paralysis causes ptosis and miosis. The attacks generally last from 15 minutes to two hours, occur one to eight times daily, and often awaken the patient after 90 to 120 minutes of sleep. The pain is excruciating in severity, and the patient commonly will pace the floor during an attack.[27]

The term "cluster" refers to the rhythm that is characteristic

of episodic cluster. While the nature of the attacks is not different between episodic and chronic cluster, the patient with chronic cluster tends to respond less well to medical therapy. Fortunately, only about 10-20% of patients meeting cluster criteria suffer from chronic cluster headache.

Cluster headache is an uncommon headache disorder, with a prevalence of about 1 in 1000 males. It usually begins between the ages of 20 and 40 years. Unlike most primary headache disorders, it is more prevalent in males, with a reported male-to-female ratio of 5:1. This ratio has changed over the past four decades, from 5.6:1 during the 1960s to 1.7:1 in the 1990s. The increase in the number of female cluster sufferers has been attributed to the increase in smoking and employment by women during this time period.[28] Cigarette smoking has been reported in 79% of episodic cluster sufferers and 88% of chronic cluster sufferers,[29] compared with about 25% of the general population.

During a cluster attack, the patient may show an ipsilateral Horner's syndrome, conjuctival injection, and tearing. The only abnormal physical sign that may be observed between cluster attacks, either permanently or for a few hours, is an ipsilateral partial Horner's syndrome.

Neurologic imaging studies such as CT and MRI are normal in patients with cluster headache.

A thorough evaluation of the headache sufferer also serves to elucidate comorbidities, drug sensitivities, or other issues that may complicate or contraindicate certain otherwise appropriate therapies. Such an appraisal is particularly pertinent to the care of the cluster patient. This individual is more apt to suffer from coronary artery disease and/or its various risk factors (hypertension, hyperlipidemia, nicotine addiction). There also may be a higher-than-expected incidence of peptic ulcer disease and alcoholism in the cluster population.

Therapy. One characterization of the current approach to cluster headache describes agents utilized for the ability to either induce a remission from the repetitive, short-lived but recurrent attacks of pain, or to maintain such a remission. Agents in the latter classification — what we will label maintenance therapies — are the foundation of the rational approach to cluster therapy. Agents described in the former category — what we will label induction therapy —, generally are effective in rapidly relieving the suffering of the cluster patient but are not suitable for long-term use. We will then describe abortive therapies, which are agents that relieve the discomfort associated with an individual attack that has proven refractory to the former two approaches.

Maintenance Therapy. The therapy of cluster headache requires an agent that is effective in preventing the volley of attacks that characterize cluster and that can be tolerated during the weeks or months occupied by the cluster period. The tolerability of such an agent often is tested indefinitely during the treatment of chronic cluster. In 1983, the efficacy of verapamil in cluster teatment was reported.[30] Based upon its utility and safety, verapamil has revolutionized the treatment of cluster (off-label use).

Bussone and colleagues compared verapamil with lithium carbonate in a double-blind crossover study in patients with chronic cluster headache. Verapamil was not only better tolerated but had a shorter latency period, with the onset of beneficial effects occurring in greater than half the patients at one week.[31] Neither drug is FDA-approved for cluster headache.

Verapamil generally is well tolerated, with few serious adverse reactions. This is particularly true when compared with the alternative agents for the treatment of cluster. The most common and troubling side effect noted clinically is constipation. Fiber supplementation and the judicious use of cathartics is warranted in this circumstance.

In episodic cluster, it often is possible to identify cluster periods that designate months that demand treatment. Mathew has suggested starting medication early in the cluster period and then tapering it slowly once the patient is free of headache for a least two weeks.[27]

Standard recommendations for the management of chronic cluster are more difficult to support by either controlled study or anecdote. An individualized approach is employed, with an attempt to slowly taper off verapamil after the patient has been cluster-free for several months. The safety of verapamil, demonstrated by indefinite use in hypertension and other conditions, permits indefinite use in the chronic cluster sufferer who does not tolerate the discontinuation of verapamil.

Lithium is an alkali metal used primarily in mood disorders. Its mechanism of action in cluster is unknown. Proposed beneficial effects in cluster include increased norepinephrine reuptake and increased serotonin receptor sensitivity. Restoration of serotonergic tone is an attractive explanation for lithium effects in cluster indirectly supported by effects demonstrated in animal brain.

Ekbom[32] is credited with the earliest report of lithium efficacy in cluster management (off-label use). Larger studies published since the original report in 1978 seem to support the same conclusions: 70% of cluster patients demonstrate a favorable response to lithium, with a greater success generally enjoyed by chronic cluster sufferers. The direct comparison of verapamil with lithium published by Bussone et al.[31] helps to explain why lithium ought to be considered an alternative to verapamil in monotherapy for cluster. The effects of lithium were realized much later than those of verapamil, with the addition of greater toxicity.[31] A potential benefit of lithium is suggested by anecdotal reports of therapeutic successes manifested by long-term remissions maintained despite the discontinuation of this agent.

The usual dose of lithium carbonate for the treatment of cluster is 600 to 900 mg/day in divided doses. Adverse reactions to lithium generally occur with levels greater than 1.5 mEq/L. Some reactions, however, including nausea, fatigue, thirst, edema, weight gain, and polyuria, may occur even with "nontoxic" levels. Tremor is quite common, although it tends to respond to either lowering the dose or the addition of beta blockers.

Ergotamine is a derivative of the rye fungus ergot (*Claviceps purpura*). Its effects upon vascular reactivity have received much attention since its application in migraine therapy in 1926.

Recently, however, attention has been drawn to its interaction with serotonin receptors. While the neurochemical model of ergotamine may be the preferred explanation for its beneficial effects, the vascular model continues to explain much of the toxicity of ergotamine. This toxicity tends to limit the use of ergotamine to rather specific circumstances in cluster therapy. While controlled trials of ergotamine in cluster headache are lacking, the clinical experiences of experts in this field suggest a role in two specific circumstances.

Ergotamine may be useful in the management of the cluster patient who suffers solely from nocturnal attacks. In this situation, a bedtime dose of 2 mg orally may be quite effective. The other accepted indication for ergotamine in cluster treatment is the patient refractory to the therapies mentioned thus far. Kudrow has found that the addition of nighttime ergotamine to daily verapamil may increase efficacy by 15%. He also has suggested that the addition of lithium to this combination may boost efficacy by an additional 5-10%.[33]

Adverse reactions are fairly common and may not mandate cessation of therapy in an otherwise desirable clinical situation. Nausea and vomiting may occur in up to 10% of patients. Other common side effects include itching, local edema, changes in heart rate, weakness, numbness, paresthesia, or pain in the extremities. Overdosage generally is seen with doses greater than 15 mg/d, although it has been reported with doses less than 5 mg. In toxic ingestion, CNS disturbances such as depression, confusion, and seizures often coexist with vasoconstriction and ischemia in a variety of locations. Drug interaction with beta blockers or macrolide antibiotics may precipitate such a toxic syndrome even in therapeutic doses.

Induction Therapy. While the use of verapamil and lithium have revolutionized the treatment of cluster headache, therapeutic benefits may not be realized for one or more weeks. For the patient who is burdened by either an active cluster period or chronic cluster, a second agent often is required during this time. As the maintenance drug begins to control the cluster headache, the induction therapy can be discontinued.

The adrenal corticosteroids and their synthetic counterparts have a variety of uses in clinical medicine. Whether their anti-inflammatory effect is the crucial activity in cluster therapy is not known. The animal evidence suggesting effects upon serotonergic pathways is an attractive explanation that may apply to the other headache types as well. The diurnal variation that characterizes physiologic steroid production suggests that steroids may be involved in some way with the human biologic clock.

In 1952, Horton published a report suggesting the utility of steroids in cluster.[34] Since that time, they have enjoyed a prominent role in the "prophylactic" treatment of cluster (off-label use). The rapid relief of symptoms obtained by their administration, their short-term safety and, alternatively, their toxicities in long-term use, all define the role of induction therapy for cluster headache. The ease of outpatient administration and low cost make them the preferred agent in this category.

Kudrow used 40 mg/day of prednisone in 92 patients suffering from cluster and obtained meaningful responses in more than 80% of patients.[33] Couch and Ziegler used variable doses of prednisone and found similar efficacy in episodic cluster, although only about half as many patients with chronic cluster responded in a similar fashion. As many as 80% of patients in this study suffered relapses of their symptoms as doses were tapered below 20 mg/day.[35] These studies demonstrate what is known of these agents from clinical experience:

- Steroids are rapidly effective, with effects often within one to two days.
- Steroids are less effective in chronic cluster.
- Attacks of cluster tend to resume as the steroid dose is tapered.

Prednisone may be the preferred agent for cluster treatment given the low cost and clinical experience with its use. Some authors do report responses with triamcinolone when prednisone is ineffective, however. The usual dose of prednisone is 40 or 60 mg/day either in a single or divided dose. Slowly reducing the dose over approximately three weeks generally is recommended to allow the selected maintenance regimen time to elicit its effects. There is some evidence that tapering to less than 10 mg/d of prednisone may be less disruptive to the pituitary-adrenal axis.

Dihydroergotamine (DHE) is a synthetic derivative of ergotamine. Raskin introduced the concept of repetitive intravenous dosing of DHE and reported success with the approach in migraine therapy in 1986.[36] Silberstein et al. applied the concept to patients suffering from chronic daily headache. While the response was impressive in the majority of patients, all 24 patients suffering from cluster obtained relief with much fewer side effects than the patients not suffering from cluster.[37] This success prompted a review of 54 cluster patients' experiences with repetitive IV DHE.[38]

All 54 patients with cluster, 28 episodic cluster patients, and 36 chronic cluster sufferers became headache-free during the IV DHE therapy. The response rate averaged approximately 30% per day of treatment. Fewer than 20% of patients experienced side effects: Eight patients reported nausea without emesis; two patients noted chest tightness without evidence of coronary ischemia; one patient reported a metallic taste in his mouth. Follow-up was provided at three, six, and 12 months, as the patients were placed on "prophylactic" (maintenance) therapy with a variety of therapies that have been previously discussed. The long-term response rates do not differ significantly from those reported for the various agents already mentioned.

Abortive Therapy. Attacks of cluster headache tend to occur despite the application of appropriate therapy. As noted, there is often a lag in the onset of efficacy of maintenance therapy. The efficacy of either induction or maintenance therapy may permit breakthrough attacks of cluster. Abortive therapies, also referred to as symptomatic therapies, shorten or abort the active cluster headache. While in general these are the safest of the cluster therapies, they are less than ideal. As they are administered upon notice of symptoms, several minutes are required for the onset of

relief. While this may shorten an individual cluster headache attack from hours to minutes, these agents generally have no effect upon future attacks. Nonetheless, these agents are important tools in allowing the cluster sufferer to cope with a less-than-optimal therapeutic regimen.

Oxygen inhalation was proposed as a useful treatment for cluster headache by Friedman and Mikropoulos in 1958.[39] In 1981, Kudrow demonstrated the efficacy of oxygen inhalation in treating 51 patients with cluster headache: 75% of patients experienced relief from at least seven of 10 attacks within 15 minutes of initiating therapy.[40] In 1985 Fogan studied oxygen in a small number of cluster sufferers in a crossover double-blind fashion using compressed air as placebo. Greater than half of those using oxygen were successful in relieving their symptoms in at least four of five attacks; only 7% of patients in the control group enjoyed similar success.[41]

The inhalation of oxygen is accepted as the safest and most effective method of aborting attacks of cluster headache. Tolerance to the effects of oxygen does not appear to be a common problem; individual attacks do tend to recur shortly after "successful" treatment, and in many cases oxygen merely postpones the attack.

The Sumatriptan Cluster Headache Study Group published a double-blind, placebo-controlled crossover trial using the subcutaneous injection of sumatriptan in 39 cluster patients.[42] Complete relief from cluster headache occurred within 15 minutes of injection in approximately half of patients.

The most frequently reported adverse reaction in studies with subcutaneous sumatriptan was local discomfort at the injection site. The incidence of adverse reactions to subcutaneous sumatriptan appears to be less in cluster patients than in migraineurs. In the Sumatriptan Study Group evaluation, there were no changes in either heart rate or blood pressure; no electrocardiographic, biochemical, or hematological anomalies were identified.[42]

Herring-Hanit[43] reported on four patients who developed a marked increase in the frequency of attacks and a prolongation in the duration of their cluster period after initiating therapy with sumatriptan.

The apparent advantages of sumatriptan in the palliative treatment of cluster headache include a high efficacy rate, speed of onset of action, and, compared with oxygen, the relatively small size of the apparatus necessary for its administration. It is therefore useful for the patient who suffers attacks outside of the home. Cost is considered the major disadvantage of this product. The recommended dose of subcutaneous sumatriptan in the acute treatment of cluster is 6 mg. This dose may be repeated once during a given 24-hour period.

Zolmitriptan nasal spray also has been shown to be effective for the relief of acute cluster attacks. It does not work as quickly as subcutaneous sumatriptan but may be easier to use or better tolerated by some patients.

Alternative Therapy for Refractory Cluster. The patient who continues to suffer from cluster headache despite the approach and measures recommended merits a trial with an alternative agent. Several alternative therapies merit consideration prior to surgical intervention.

Hering and Kuritzky published encouraging results of an open trial of sodium valproate (off-label use) in 15 cluster patients.[44] Side effects of this agent include drowsiness, tremor, nausea, vomiting, hair loss, and weight gain. The dose of sodium valproate generally lies between 600 mg and 2000 mg/day in divided doses. Periodic assessment of serum levels is necessary to maintain levels in the target range of 50 to 100 micrograms per milliliter. Monitoring of liver function and complete blood count is recommended at periodic intervals. It is contraindicated in patients with liver disease.

Topiramate has been evaluated in a series of open-label studies in the prevention of cluster headache (off-label use). Preliminary results were encouraging; however, more methodically rigorous trials are needed to establish its role in cluster therapy.[45]

Preliminary reports of the efficacy of intranasal capsaicin (off-label use) are encouraging. As application to the naris contralateral to that of symptoms is ineffective in cluster, the mechanism of action is presumed to be the depletion of pain-producing polypeptides (substance P) in the peripheral nerves.[46] The optimal dosage schedule has not been elaborated.

Intravenous histamine desensitization (off-label use) has been used to manage intractable cluster headache. Up to two-thirds of patients noted a 50% or greater reduction in cluster frequency after this therapy. Melatonin (investigational use) is being studied for the treatment of cluster headache.

Analgesic Medication Overuse

An extremely important condition contributing to the development of headaches in a chronic daily pattern is overuse of analgesic medication. This is most likely to occur in patients with frequent headaches. Analgesic overuse was reported in 25-38% of the chronic daily headache population.[47] In headache referral centers, rates of analgesic overuse range from 46% to 87% of chronic daily headache sufferers.[47]

Medication-overuse headache is defined as headache occurring during the frequent use of symptomatic headache medication or chronic intake of other substances, as well as headache occurring in the withdrawal phase after such substance use.[4,48] The headache is daily or almost daily and disappears within a few weeks of medication withdrawal. Headache induced by chronic medication use occurs after daily doses of an acute treatment medication for at least three months. There is no compelling scientific research that simple analgesics such as aspirin, acetaminophen, or NSAIDs induce headaches with daily use, and some evidence that daily NSAID or aspirin use may reduce headache frequency.[19,49-51]

Medication-overuse headache in migraine patients presents as a constant, diffuse, dull headache without associated symptoms.[48] Clinically, this syndrome cannot be differentiated from migraine with chronic tension-type headache or chronic migraine. Withdrawal headache in migraine patients resembles a

severe and prolonged migraine attack. In patients with chronic tension-type headache or post-traumatic headache, medication overuse headache cannot be discriminated from the characteristics of the primary headache.[48]

Daily use of triptans or ergots may lead to a throbbing, pulsating headache in the early morning, sometimes with nausea. The headache disappears between 30 and 60 minutes after intake of a triptan or ergotamine. It may be distinguished from migraine by the absence of an attack pattern or associated migraine symptoms.[48]

In their meta-analysis of studies on chronic medication overuse headache, Diener and colleagues[48] found that 65% of patients had migraine as their underlying headache disorder, while 27% had tension-type headache and 8% had mixed headache. Women were 3.5 times as frequent as men to suffer with chronic medication overuse headache. Patients developing chronic medication overuse headache had an average duration of primary headache exceeding 20 years and frequent drug intake for greater than 10 years. The mean duration of daily headache was almost 6 years. Patients used either combination drugs or multiple products, averaging 2.5 to 5.8 different pharmacologic components taken simultaneously.

Drug Habituation and Detoxification

Drug habituation may accompany many chronic headache syndromes. Analgesic overuse must be considered early in patient management. Medications that are known to cause medication-overuse (rebound) headaches include opiates, barbituates, triptans, ergotamine tartrate compounds, benzodiazepines, and caffeine preparations.[18] Discontinuation of habituating drugs should be the initial step in the treatment of patients who are taking excessive pain medications (i.e., using daily or almost daily habituating pain medication or taking ergotamine or triptans more than twice weekly). Prophylactic medication may be less effective in patients suffering from medication-overuse headaches. Frequently, patients will say that they "would stop taking pain medication if only the preventive medication prevented the headaches." Patients must be instructed that the pain medication is part of the cause of the headaches and that headache therapy is futile until the habituation cycle is resolved. Typical analgesic withdrawal symptoms last 2-10 days (average 3.5) and include headache, nausea, vomiting, hypotension, tachycardia, sleep disturbances, restlessness, and anxiety. Seizures and hallucinations are rare, even for patients using barbiturate-combination drugs.

Management of the habituated patient can be difficult, and the medical literature offers limited insight into proper techniques of detoxification. Hering and Steiner[52] reported successful outpatient management of patients with medication-overuse headache using the technique of: abrupt drug withdrawal; explanation of the disorder; regular follow-up; amitriptyline 10 mg at bedtime for prophylaxis (off-label use); and naproxen 500 mg for acute relief (off-label use). Smith[53] reported an effective outpatient treatment plan for analgesic rebound headache that included: abrupt drug withdrawal; tizanidine 2 mg at bedtime, titrated every 3 to 5 days to 2 to 16 mg at bedtime (off-label use); and a long-acting NSAID in the morning.

Patients who are habituated to opioids may benefit from clonidine to prevent physical signs and symptoms of withdrawal (off-label use). In the absence of good scientific evidence, glucocorticoids and phenothiazines sometimes are prescribed for outpatient detoxification from butalbital, ergotamine, or low doses of opioids (off-label use). Generally, a six- to 14-day tapering course of glucocorticoid is given, with phenothiazine suppositories prescribed for severe withdrawal headaches associated with vomiting. For patients with concomitant medical problems, a history of seizures, or prior unsuccessful outpatient detoxification, inpatient detoxification may be required. Prevention of relapse after detoxification is critical to prevent recurrence. About one-third of patients will relapse into drug overuse within the first five years after detoxification. Almost 90% of patients who relapse use the same drug that they initially overused.[48]

An approach to reduce relapse should include the following:

- Use specific antimigraine drugs only for migraine attacks.
- Restrict the dose of ergots and triptans per attack and per week.
- Avoid mixed analgesics, butalbital, opioids, and tranquilizers.
- Start prophylactic drugs early (> 2-3 attacks/month).

Treatment of Chronic Daily Headache

The first step in the treatment of the chronic daily headache syndrome is to split the problem into manageable headache components. While there is no specific treatment for chronic daily headache, there are potentially effective approaches for medication-overuse headache, chronic tension-type headache, and migraine. The management approach may include treatment of the analgesic overuse by abrupt analgesic withdrawal, prophylactic therapy for the chronic tension-type headaches, and abortive and prophylactic therapy for the migraine attacks.

In clinical practice, it is not uncommon to see improvements in some components of the headache syndrome and intractability in other components. After drug withdrawal and initiation of abortive and prophylactic therapies, patients may improve in their ability to manage their acute migraine attacks but continue to be burdened by the frequency of their migraine or tension-type headache attacks. Their quality of life and functional ability often is significantly improved, yet they still may report having frequent headaches. Practitioners should rely on quality of life or functional (disability) measures, rather than number of headache days, to judge the outcome of therapy. Only by splitting the chronic migraine into its component parts can the practitioner modify therapy to improve the poorly controlled component(s) without giving up the gains achieved in other aspects of the headache syndrome.

Even though chronic tension-type and chronic daily headache are common, very few well-controlled studies of their treatment have been done. Most of the studies have been limited by small numbers of patients and short duration of therapy.

There are no drugs currently approved by the FDA specifically for the treatment of chronic tension-type or chronic daily headache. However, given the chronic nature of the disorder and the risk of medication overuse headache in patients with frequent headaches, prophylactic therapy seems warranted for most patients. Since chronic headache is a disorder of central pain processing, medications with central pain modulating effects (antidepressants and anticonvulsants) tend to be the most effective.[13]

Counselling and Compliance

It is estimated that nearly half of all migraine sufferers have given up seeking help for their headaches from their physicians. Although patients sometimes find their headache medications to be ineffective, it is physician behavior toward the headache patient that discourages continuity of care. Counselling the patient on the mechanisms of headache, trigger factors, expected outcome of therapy ("control" of headaches and improvement in lifestyle without "cure" of disease), and reassurance of the absence of serious disease should help to cement the therapeutic relationship. Further discussion on the wide varieties of medications available to aid the headache sufferer should encourage the patient to continue care if the initial therapy is ineffective or poorly tolerated. When the patient and physician have developed a relationship based on an understanding of the disease, the patient's response to her or his illness, knowledge of the risks, benefits, and goals of therapy, compliance rarely is a problem. Limiting the dietary and lifestyle restrictions (reduction of trigger factors) to those that apply to a given patient will improve compliance. For example, a woman who gets migraines only with menses should not be asked to eliminate chocolate and cheese from her diet. Patients with cluster headache must eliminate alcohol during the cluster cycle, but abstinence between cycles will not influence the headache pattern. Smoking cessation, however, may benefit the headache problem. The physician treating headache patients must be available to handle the episodic exacerbations of headache and the occasional headache that does not respond to usual medications. Additionally, the patient and physician must forge a long-term relationship to deal with the chronic nature of headaches.

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Primary Care Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

• summarize recent, significant studies related to the practice of primary care medicine;

• evaluate the credibility of published data and recommendations related to primary care medicine;

• discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a credit letter. When your evaluation is

337:1442-1443.
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Physician CME Questions

26. The primary headache more common in men than women is:
    A. migraine
    B. chronic tension-type
    C. cluster
    D. medication overuse headache

27. Triptan treatment should:
    A. be given as needed for pain
    B. be avoided in patients with known coronary artery disease
    C. be prescribed for tension-type headache
    D. all of the above

28. Palliative therapy for cluster headache includes:
    A. oxygen
    B. zolmitriptan nasal spray
    C. sumatriptan injection
    D. all of the above

CME Answer Key

26. C; 27. B; 28. D

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2. Summarize recent, significant studies related to the practice of primary care medicine.	⬭	⬭	⬭	⬭	⬭	⬭
3. Evaluate the credibility of published data and recommendations related to primary care medicine.	⬭	⬭	⬭	⬭	⬭	⬭
4. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.	⬭	⬭	⬭	⬭	⬭	⬭
5. The test questions were clear and appropriate.	⬭	⬭	⬭	⬭	⬭	⬭
6. I detected no commercial bias in this activity.	⬭	⬭	⬭	⬭	⬭	⬭
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If so, how? _____

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PPIs and Clopidogrel: Do We Have to Worry?

Source: O'Donoghue ML, et al. *Lancet* 2009;374:989-997.

THE ANTIPLATELET EFFECT OF CLOPIDOgrel is dependent upon its conversion and activation through the 2C19 pathway of the P450 system. Blockade of this pathway occurs because of genetics, in persons who do not have sufficiently active 2C19, and pharmacotherapies that specifically block 2C19. Proton pump inhibitors (PPIs), particularly omeprazole, are recognized to be 2C19 inhibitors. Is there reason for concern?

Although the in vitro aspects of PPI-antiplatelet interactions are of interest, it is probably more important to see whether such interactions affect the bottom line: CV events. Fortunately, there is a large — and largely reassuring — database from which to glean the impact of the PPI-antiplatelet interaction.

The PRINCIPLE-TIMI and TRITON-TIMI are acute coronary syndrome trials in which clopidogrel and/or prasugrel were used. In both of these trials, some participants were also using PPIs, providing an opportunity to see if concomitant utilization of a platelet inhibitor and PPI affected outcomes.

Subjects who were on clopidogrel who also were receiving PPIs showed less effective platelet inhibition compared to clopidogrel alone (in vitro testing). This effect was less pronounced among prasugrel recipients, consistent with its lesser dependence upon the P450 system for full activity.

Although platelet aggregometry demonstrated diminished antiplatelet effect, in these 2 trials (total n > 15,000), there was no signal of increased adverse outcomes in subjects concomitantly receiving a PPI and clopidogrel or prasugrel. PPIs provide important GI protection for persons on NSAIDs, as well as excellent symptomatic relief for GERD patients. These data suggest that PPIs need not be avoided when treating acute coronary syndromes with clopidogrel or prasugrel. ■

Surgery vs Medical Treatment for CTS

Source: Jarvik JG, et al. *Lancet* 2009; 374:1074-1081.

SEVERAL TRIALS COMPARING SURGICAL with medical therapy for carpal tunnel syndrome (CTS) have been insufficient to clarify the optimum approach. Similarly, it is largely unknown which CTS characteristics predict a favorable response to either type of treatment. Jarvik et al conducted a controlled trial of CTS patients (n = 116) randomized to medical or surgical treatment. Additionally, wrist MRI and nerve conduction studies were performed to identify the predictive capacity of these metrics.

Surgical intervention consisted of either open or endoscopic carpal tunnel decompression (per surgeon preference). Medical treatment included ibuprofen 200 mg tid, physical therapy provided by a hand therapist, other analgesics, corticosteroid injections, and ultrasound (all as per clinician preference). The primary outcome was function as measured by the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) at 12 months.

There were no serious adverse events in either treatment group. At 12 months, although both groups showed substantial improvement, the CTSAQ score was significantly better in the surgical group. Study subjects with baseline nerve conduction deficits responded less well to surgical intervention. On MRI, patients with signs of nerve edema (indicative of more advanced disease severity) had successful outcomes (30% improvement on the CTSAQ) only half as often as those without edema. In patients with more severe baseline disease, difference in outcome between surgery and medical management diminished. Overall, surgical intervention provides outcomes that are superior to medical therapy. MRI and nerve conduction data may assist patient selection. ■

Influenza Vaccine: Flu Shot vs Nasal Mist

Source: Monto AS, et al. *N Engl J Med* 2009;361:1260-1267.

IS INFLUENZA MANAGEMENT GETTING more complicated, or is it just me? Dealing with vagaries of virus antigenic shift and drift, the moving target of antiviral resistance, insufficiently sensitive point-of-care testing for influenza, and the ever-evolving designation of appropriate risk groups for "seasonal" (regular) vs "novel" (pandemic) influenza prevention is a daunting challenge.

Two major categories of trivalent influenza vaccine are available to prevent seasonal flu: inactivated (SHOT) and live attenuated (NASAL). A randomized double-blind placebo-controlled trial compared the efficacy of SHOT and NASAL vaccine to prevent influenza. Adults 18-49 years (excluding persons with contraindications to

live vaccine) received one vaccine or placebo, and recorded respiratory symptoms through the 2007-2008 flu season; throat swabs were obtained for confirmation of influenza during periods of respiratory symptoms.

Among the 1963 subjects, 6.1% experienced laboratory-confirmed influenza. SHOT efficacy vs placebo was 68% compared to NASAL efficacy of 36%. In the 2007-2008 influenza season, risk reduction of influenza was almost twice as great with SHOT. ■

Beleaguered Primary Care Clinicians

Source: Krasner MS, et al. *JAMA* 2009; 302:1284-1293.

IF DATA OBTAINED WITHIN THE LAST 5 years are correct, the majority of primary care physicians (PCPs) report emotional exhaustion, depersonalization, and/or low sense of accomplishment — collectively called burnout. The favorable results of an intervention to alleviate burnout deserves our focus.

Primary care physicians (n = 70) in Rochester, NY, participated in a year-long intervention: 8 weeks of intensive intervention, followed by once-monthly maintenance for 10 months. Although the complexity of intervention was too great to be captured in this communication, didactic materials (including presentations on dealing with conflict, reflecting on meaningful experiences, etc.), meditation (including yoga-type exercises), and narrative exercises (for instance, writing and sharing brief stories about challenging experiences in practice) were included. Sessions occupied 2.5 hours/week for 8 weeks, followed by monthly maintenance 2.5-hour sessions for 10 months. A single all-day session of mindfulness meditation was included during week 6-7.

Following the intervention, scores on the Maslach Burnout Inventory showed meaningful improvements. Although this is a time-intensive investment, it is encouraging to see tools through which clinicians might better enjoy, be better fulfilled by, and probably perform more effectively in their practice. ■

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Beyond Diabetes Prevention

Source: Perreault L, et al. *Diabetes Care* 2009;32:1583-1588.

MOST INDIVIDUALS WITH PREDIABETES, defined as either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, will go on to develop diabetes unless an intervention is instituted. To date, diet, exercise, and pharmacotherapy have all been shown to reduce progression to diabetes by as much as 60%, with diet + exercise being the clearest winner. Although prevention (or delay) of diabetes is important, many persons who do not progress to overt diabetes during a diabetes prevention trial remain prediabetic, which is still a high-risk category. The report by Perreault et al describes factors which were associated, during intervention for diabetes prevention, with restoration to normal glucose regulation.

The Diabetes Prevention Program was the largest diabetes prevention trial to date (n = 3234). Prediabetes subjects were randomized to intensive lifestyle intervention (diet + exercise), metformin (850 mg bid), or placebo, with a mean follow-up of 3 years.

Within the categories of impaired fasting glucose (glucose = 100-125 mg/dL) and impaired glucose tolerance (glucose = 140-199 mg/dL on oral glucose tolerance testing), persons with lesser baseline impairments were more likely to enjoy restoration to normal glucose regulation. Similarly, younger subjects and those who successfully lost weight regained euglycemia more often.

We can encourage our patients that efforts to prevent diabetes can do that and, in some cases, even restore glucose regulation to normal. ■

Does Metformin Affect Thyroid Function?

Source: Cappelli C, et al. *Diabetes Care* 2009;32:1589-1590.

DIABETES COMMONLY IS COMORBID with other endocrinopathies, including hypothyroidism and hypogonadism. The most common first-line pharmacotherapy for diabetes is metformin, which has been heretofore been considered an essentially benign drug, when proscriptions for its use (e.g., renal insufficiency, heart failure) are observed. Recent reports have suggested that metformin might have an effect on TSH even when levothyroxine replacement doses are kept constant; since many hypothyroid patients are diabetic, such effects may be worthy of note.

Capelli et al evaluated in a pilot study 11 diabetic patients with hypothyroidism who initiated therapy with metformin. All had been on stable doses of levothyroxine. Thyroid studies (TSH, free T4 and T3, and total T4 and T3) were performed at baseline, 6 hours, 24 hours, 72 hours, and 3 and 6 months after initiation of metformin. They included in their analysis additional data from another study population comprised of diabetics receiving thyroid for various indications, diabetics with subclinical hypothyroidism not receiving levothyroxine replacement, and diabetics with normal thyroid function.

During the pilot study, despite continued stable levels of levothyroxine replacement and other thyroid parameters, the mean TSH dropped from 2.11 to 1.5 mIU/L. Omission of metformin in one patient who had experienced a more dramatic TSH decline resulted in a return of TSH to baseline. Particularly in the diabetic group with subclinical (non-replaced) hypothyroidism, the decline in TSH was apparent: from a mean of 4.5 to 2.93 mIU/L at 1 year. The mechanism by which metformin lowers TSH is not known. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Insulin Regimens in Type 2 Diabetes

In this issue: Efficacy of once-daily insulin, aldosterone use in heart failure, erectile dysfunction Clinical Practice Guidelines, and FDA Actions.

Efficacy of once-daily insulin

Most type 2 diabetics, even those on oral medications, will eventually require insulin for glycemic control. A new study suggests that simple once-a-day insulin may be as effective as more complex regimens. Researchers from England evaluated 708 patients who had suboptimal hemoglobin A1c (HbA1c) levels while taking metformin and a sulfonylurea.

Patients were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily with an increase to twice daily if needed. Sulfonylurea therapy was replaced by a second type of insulin if hyperglycemia became unacceptable during the first year of this study or if HbA1c levels were > 6.5%. Outcomes measures were HbA1c levels, the proportion of patients with HbA1c ≤ 6.5%, the rate of hypoglycemia, and weight gain. After 3 years, median HbA1c levels were similar in all 3 groups. More patients had HbA1c levels < 6.5% in the prandial and basal groups, although more than 80% of patients in the basal group required a second type of insulin. The median number of hypoglycemic events per patient per year during the trial was lowest in the basal group (1.7) compared to the the biphasic (3.0) and prandial (5.7) groups ($P < 0.001$). Weight gain was highest in the prandial group. The authors conclude that the basal or prandial insulin-based regimens added to oral therapy resulted in better HbA1c levels compared to a biphasic insulin regimen. In addition, the basal group also had fewer hypoglycemic episodes and less weight gain. The authors state that the "results support the initial addition of a basal insulin to oral therapy, with subsequent intensification to a basal-prandial regimen..." (published at www.nejm.org Oct. 22, 2009).

In an accompanying editorial, Michael Roden, MD, points out that regardless of group, most subjects were accelerated to multiple doses of insulin per day. The study was sponsored by a manufacturer of insulin analogues, and only their analogue products were used in the study, whereas current consensus statements recommend regular human insulin. The editorial also points out that blood sugar control is only part of the equation with diabetics. Aggressive blood pressure control and use of statins and aspirin are equally important. Still, more studies are suggesting an early intensification of treatment with insulin may effectively reduce complications in type 2 diabetes (published at www.nejm.org Oct. 22, 2009).

For updated guidelines on the treatment of type 2 diabetes, see the recently released one-page algorithm from the American Association of Clinical Endocrinologists: www.aace.com/pub/pdf/GlycemicControlAlgorithm.pdf. ■

Aldosterone use in heart failure

Aldosterone antagonists are underused in

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patients with moderate-to-severe heart failure (HF) and systolic dysfunction according to a new study in the *Journal of the American Medical Association*. Aldosterone antagonists (spironolactone and eplerenone) have been shown to be very effective in the treatment of HF such that they were designated class I (useful and recommended) in the recent American College of Cardiology/American Heart Association Chronic HF Guidelines. Despite this, the drugs are underused in eligible patients.

The current study was an observational analysis of more than 43,000 patients admitted to the hospital with HF and discharged home from 241 hospitals participating in the Get With The Guidelines — HF quality improvement registry between 2005 and 2007. Among 12,565 patients eligible for aldosterone antagonist therapy, only 4087 (32.5%) received one of the drugs at discharge. There was wide variation in aldosterone antagonist usage among hospitals (0%-90.6%) and was more likely to be used in younger patients, African Americans, those with lower blood pressure, history of implantable cardioverter-defibrillator, depression, alcohol use, pacemaker implantation, and those having no history of renal insufficiency. Inappropriate use of aldosterone antagonist therapy was low. The authors conclude that use of aldosterone antagonist therapy is underutilized in HF patients, occurring in only one-third of eligible patients, although the rate of use increased gradually throughout the course of the study. They also state that use of evidence-based guidelines in hospitals may be warranted to improve treatment of HF patients (*JAMA* 2009;302:1658-1665).

Many clinicians shy away from use of aldosterone antagonists because of concerns regarding hyperkalemia, especially since many of these patients are also on ACE inhibitors or ARBs. Aldosterone inhibitor use in HF is not part of the Joint Commission/Centers for Medicare and Medicaid Services core performance measures. Regardless, aldosterone antagonists have been shown to benefit patients with HF and they are clearly underutilized. ■

Erectile dysfunction guidelines

The American College of Physicians has published a Clinical Practice Guidelines regarding hormonal testing and pharmacologic treatment of erectile dysfunction (ED) in men. The guideline recommends that clinicians initiate therapy with a PDE-5 inhibitor (sildenafil, vardenafil, or tadalafil) in men who seek treatment for ED and do not have a contraindication such as concomitant nitrate use. They rate this a strong recommendation with high-quality evidence. The choice of a PDE-5 should be based on preference, including ease of use, cost, and adverse effects profile. The guideline does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction due to insufficient evidence to determine benefits and harm. The guideline reviewed more than 100 randomized controlled trials that showed that PDE-5 inhibitors improved successful sexual intercourse and improved erections in men with ED (*Ann Intern Med* 2009 Oct 19;). ■

FDA Actions

The FDA has authorized emergency use of IV antiviral peramivir for treatment of 2009 H1N1 influenza in hospitalized patients. The drug is not yet approved for use in this country, but was authorized in response to a request from the CDC. IV peramivir is approved only for hospitalized adult and pediatric patients for whom an IV drug is clinically appropriate because the patient is not responding to either oral or inhaled antiviral therapy, because enteral or respiratory therapy is not feasible, or in adults when a clinician judges that IV therapy is appropriate due to other circumstances. This is the first available IV antiviral available for 2009 H1N1 infections. For more information see www.cdc.gov/h1n1flu/eua/.

The FDA has approved the quadrivalent human papilloma virus (HPV) vaccine (Gardasil®) for use in boys and young men. The vaccine is approved for males ages 9-26 as 3 injections given over a 3-month period. HPV is the most common sexually transmitted disease in the United States with 1 of 500 men infected every year. Previously, the vaccine had only been approved for use in females ages 9-26 years. In related news, a recent study from the National Cancer Institute, CDC, and American Cancer Society has suggested that the vaccine is not cost-effective for women older than age 30 who undergo annual or biennial screening for cervical cancer (*Ann Intern Med* 2009;151:538-545). Similarly, a study from Harvard found that HPV vaccination for 12-year-old girls was cost-effective, but the same vaccination for 12-year-old boys was not (*BMJ* 2009 Oct. 8).

The FDA has also approved a bivalent HPV vaccine for use in females, which protects against HPV types 16 and 18. The vaccine is being marketed as a "cervical cancer vaccine" by GlaxoSmithKline under the trade name Cevarix®. ■