Refractory Migraine

Rational Combination Therapy in Refractory Migraine

B. Lee Peterlin, DO; Anne H. Calhoun, MD; Sherry Siegel, MD; Ninan T. Mathew, MD

Refractory migraine (RM) headaches pose important treatment challenges to the patients who live with them and the clinicians who try to treat them. Defined based on the lack of response to acute, preventive, and nonpharmacologic treatment, RM is often treated with a combination of treatments. Although combination therapy for RM has not been systematically studied in randomized trials, clinical experience suggests that a rational approach to RM treatment, utilizing a combination of treatments, may be effective where monotherapy has failed. In this article we briefly identify patient populations appropriate for more aggressive migraine prevention with combination therapy. We then discuss modifiable risk factors and comorbidities in migraine and then focus on the use of rational combination therapy, as well as the duration migraine preventatives should be considered for use. Future research is needed to evaluate the full potential of rational combination treatment as a strategy for treating and ultimately preventing RM.

Key words: refractory migraine, chronic migraine, headache, migraine, rational combination therapy, migraine prevention

(Headache 2008;48:805-819)

Migraine is estimated to affect approximately more than 30 million people in the United States alone.1 While the prognosis for the majority of patients is good, approximately 3-14% of episodic migraineurs will progress to chronic daily headache.2,3 And unfortunately, it has been estimated that only 14% of chronic daily headache sufferers will remit to less than one headache per week over one year.2 Thus, while migraine itself confers substantial personal and societal burden, refractory migraine (RM) may extract an even greater toll.1,4,5 (The definitions and the epidemiology of RM and refractory chronic migraine are reviewed elsewhere in this series of articles [Schulman et al, 2008; Lipton and Bigal, in this issue]).

Although data suggest that effective acute treatment of migraine is associated with improved responses and decreased disability, the potential disease-modifying effects of migraine preventives have not been studied.6,7 It is plausible that migraine preventives may possess such effects, as several neurological disorders with pathophysiological similarities to migraine (including multiple sclerosis and epilepsy) have data suggesting preventative therapy limits disease burden, ie, results in “disease modification.”8-10 Ultimately, our goal should be to prevent the development of RM. However, RM is defined by a poor response to both pharmacologic and nonpharmacologic treatment. Thus, in RM sufferers it is natural to consider combination preventive treatment for this group of patients. And herein, we will focus on the treatment of developed refractory disease.

Conflict of Interest: None
In this article, we will first briefly identify patient populations that may be appropriate to consider for combination preventative therapy. We will then focus on potentially modifiable factors in migraine and discuss the use of rational combination therapy for migraine prevention – with the caveat that none of these combinations are approved by the Food and Drug Administration. Finally, we will briefly discuss the appropriate duration for preventive therapy.

It should be noted that where possible the combination of preventatives that are reviewed are based on the available data utilizing polytherapy in migraine. However, as research in migraine polytherapy is in its infancy, most of the suggestions are based on the evidence of randomized controlled trials of medications showing efficacy for migraine prevention as monotherapy, combined with anecdotal evidence and the authors’ personal experience. It should also be recognized that many other effective combinations exist which are not reviewed here. However, a review of every potential combination therapy that can be utilized for migraine prevention is beyond the scope of this article.

WHEN TO CONSIDER COMBINATION THERAPY

Concurrent risk factors and/or comorbidities frequently guide preventive choices and may warrant consideration of combination therapy. Several psychiatric disorders (including depression, anxiety, and bipolar disorder) and medical disorders (including stroke, epilepsy, asthma, and cardiovascular disease) are comorbid with migraine.\textsuperscript{11,12} Additionally, other factors are associated with migraine chronication. While some of these risk factors, including age and gender, are not modifiable, others such as obesity and medication overuse are.\textsuperscript{13,14} And although we recognize that monotherapy may be preferred for preventative therapy, clinically this may not always be attainable.

A clinic-based study by Oates et al found that 69% of headache patients were on one or more medication that was not intended for headache prevention.\textsuperscript{15} Many of these non-headache prescriptions were substances that impacted preventative therapy such as hormones, antidepressants, and antihistamines. This emphasizes the importance of obtaining a complete medication history (along with the indications for these drugs). It may be possible to utilize one drug for dual therapeutic purposes, and medications which could thwart successful headache management may be identified.

Migraine preventives are predominantly from one of 3 drug classes: antiepileptic, antidepressant, and antihypertensive agents.\textsuperscript{16-18} However, other classes have data supporting efficacy in migraine prevention, including antihistamines, hormonal agents, dopamine antagonists, nonsteroidal anti-inflammatory agents, and some vitamins or supplements.\textsuperscript{16-23} Choice of preventives may be based on the presence or absence of comorbidities or risk factors. However, in the absence of prospective longitudinal data, migraine-specific combination therapy is largely anecdotal and based on clinical experience. And though unproven, factors including a strong family history and an earlier age of onset may warrant consideration for migraine-specific combination therapy.\textsuperscript{4,5} In consideration of the proposed criteria for RM by the Refractory Headache Special Interest Section (RHSIS) of the American Headache Society (Table 1), we suggest consideration of combination therapy based on: (1) disability and (2) history of repetitive failure of previous preventives.

The proposed RHSIS RM criteria include failure of at least 2 preventive medications from 2 different classes; these patients warrant consideration of preventative polytherapy, a suggestion that is supported by 2 studies.\textsuperscript{24,25} The first was an open-label study of 52 RM patients, evaluating the effectiveness of either a β-blocker, or valproic acid alone as compared with the 2 drugs in combination.\textsuperscript{24} The majority (75%) of participants had previously failed a trial with amitriptyline or flunarazine. Participants were then given a 2-month trial with a β-blocker alone. In subjects who showed no response to the β-blocker, a 2-month trial of valproic acid alone was given. Participants who still failed to respond were then treated with combination therapy. Over half (56%) of the patients showed a >50% reduction in migraine headache days while only 29% showed no response; 15% stopped therapy.
secondary to adverse events. These results are notable, as over three-quarters of participants had failed monotherapy with 3 pharmacological agents from 3 different classes before successful migraine prevention was achieved with polypharmacy.

More recently, Pascual et al evaluated the use of a β-blocker plus topiramate in RM patients. Participants had previously failed monotherapy with each medication. Of the 58 patients evaluated, approximately 60% of participants showed >50% reduction in headache frequency, while 17% did not tolerate the combination. In addition, among responders, 44% showed an excellent (>75%) response. These studies suggest that combination therapy may benefit a subgroup of patients who would be classified as refractory migraineurs by the RHSIS RM criteria. Further research is warranted to confirm these results and identify potential populations in which combination therapy may be appropriate.

### RATIONAL COMBINATION THERAPY: PREVENTIVE COMBINATIONS TO CONSIDER

Guidelines do not currently exist for combination therapy in migraine. Nevertheless, logic suggests that certain combinations may be useful, particularly in RM. And although a review of every combination that may be appropriately used in migraine prevention is beyond the scope of this article, we will review some options for consideration. It should be noted that where possible these options will be based on the available clinical studies utilizing polytherapy for migraine prevention. However, due to the extreme paucity of research in this area to date, the following combinations are largely based on monotherapy randomized controlled studies showing efficacy for migraine prevention, anecdotal evidence, and the authors’ personal experience (Table 2).

#### β-Blockers—Mechanism of Action

The mechanism by which β-blockers benefit migraine is not entirely known; and the known actions vary significantly among different β-blockers. Some, like propranolol, have membrane stabilizing activity, possess affinity for 5-HT sites in the brain, and inhibit cytokines; yet efficacy in migraine prevention has been shown with β-blockers (such as timolol), which do not share these properties. Given their varied mechanisms, the only identified common property of β-blockers that are successful in migraine prevention is their lack of partial agonist or intrinsic sympathomimetic activity.

#### When to Consider β-Blockers for Combination Therapy

In patients who inadequately respond to monotherapy with another class of preventive – such as an antiepileptic or antidepressant – the addition of a β-blocker may be considered. There is evidence that the combination of a β-blocker and an antiepileptic (either valproic acid or topiramate) is effective in RM – even in the absence of response to the β-blocker alone (as reviewed above). Additionally, in hypertensive migraineurs or those with performance anxiety or aggressive behavior, the addition of propranolol may be considered. Although β-blockers are first-line choices for hypertensive patients with angina, they are not first-line therapy for coronary artery disease prevention (Table 3).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary indications</th>
<th>Adverse events</th>
<th>Selected contraindications and precautions</th>
<th>Relative indications (based on comorbidities &amp; risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Depression; social phobia; anxiety and panic disorders; enuresis</td>
<td>Fatigue, dry mouth and other anticholinergic effects, arrhythmias, weight gain</td>
<td>Heart block and significant arrhythmia, concomitant MAOIs, glaucoma, hypertension</td>
<td>Anorexia, neuropathic pain, insomnia</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Depression</td>
<td>Dizziness; drowsiness; dry mouth; headache; impotence; nausea; sensitivity to sunlight; sweating; weight loss or gain</td>
<td>Concurrently concomitant with a MAOI</td>
<td>Anorexia, neuropathic pain</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Depression</td>
<td>Anxiety, confusion, dizziness, flushing, headache, impotence, insomnia, low blood pressure, rapid heartbeat, rash, seizures, GI symptoms</td>
<td>Acute recovery phase of MI; co-administration with cisapride; use with caution in history of seizure, urinary retention</td>
<td>Obesity, europathic pain, fatigue</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Depression, GAD, social anxiety disorder; panic disorder</td>
<td>Increased blood pressure, abnormal ejaculation/ orgasm, anxiety, blurred vision, constipation, dizziness, dry mouth, impotence, insomnia, nausea, nervousness, sedation, sweating, tremor, weakness, weight loss constipation, headache, insomnia, nausea, sweating</td>
<td>Gradual taper when discontinuing, nausea, dry mouth, anorexia, dizziness, sweating somnolence, abnormal ejaculation, impotence in men, anorgasminia in women, decreased libido, insomnia, nervousness, tremor, hypertension, yawning</td>
<td>Obesity, PMS/PMDD</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Diabetic peripheral neuropathic pain; generalized anxiety disorder; major depressive disorder</td>
<td>Cough, diarrhea, dizziness, dry mouth, frequent urination, headache, loss of appetite, muscle aches, nausea, drowsiness, sleeplessness, sweating</td>
<td>Uncontrolled narrow-angle glaucoma; with MAOI; hypersensitivity</td>
<td>Diabetic neuropathic pain</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Anxiety disorders</td>
<td>Dizziness, nausea, headache, lightheadedness, agitation, insomnia</td>
<td>Hypersensitivity</td>
<td>Anxiety + β-blocker</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil, flunarazine (not available in the United States)</td>
<td>Angina, arrhythmias, hypertension</td>
<td>Constipation, hypotension, AV block, edema, nausea</td>
<td>Severe LVD, hypotension (systolic pressure &lt; 90 mmHg) cardiogenic shock, sick sinus syndrome (exception: ventricular pacemaker), second- or third-degree AV block (exception: ventricular pacemaker), atrial flutter or fibrillation and accessory bypass tract (eg, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes)</td>
<td>Hypertension, hemiplegic migraine, Vitamin B2, Coenzyme Q10, Topiramate, Aspirin, Amitriptyline, Magnesium</td>
</tr>
<tr>
<td>β-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol, Timolol; Nadolol; others</td>
<td>Hypertension, angina, migraine prophylaxis, hypertrophic subaortic stenosis</td>
<td>Fatigue, heart failure/block, lightheadedness, hypotension, cold extremities, depression, bronchospasm, impotence, weight gain, masking of hypoglycemia</td>
<td>Sinus bradycardia and greater than first-degree block; cardiogenic shock; congestive heart failure, asthma and obstructive pulmonary disease; bronchospasm, diabetes &amp; hypoglycemia, thyrotoxicosis, Wolff-Parkinson-White, peripheral vascular disease, headache with focal neurological symptoms</td>
<td>Mitral valve prolapse, hypertension, angina, performance anxiety, aggressive behavior, + Valproic acid, + Topiramate, Note: Duloxetine + propranolol may cause increased β-blockade</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Epilepsy</td>
<td>Weight loss, nephrolithiasis, glaucoma, sedation cognitive dysfunction, paresthesias</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Epilepsy</td>
<td>- Neuropathic pain; borderline personality disorder + TCA in diabetes + Lithium for bipolar disorder - Bipolar disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Epilepsy</td>
<td>Pancreatitis, increased liver enzymes, hepatitis, neural tube defects, agranulocytosis, GI symptoms, asthenia, sedation, tremor, hair loss, weight gain</td>
<td>Agranulocytosis, liver disease, pregnancy or risk of pregnancy, urea cycle disorders</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Epilepsy; post-herpetic neuralgia</td>
<td>Sedation, dizziness, unsteady gait, fatigue</td>
<td>Hypermobility</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Epilepsy</td>
<td>Nausea, sedation, cognitive dysfunction, ataxia</td>
<td>Unusual thoughts or behavior; anxiety, hallucinations; agitation; chills, flu symptoms; weakness, dizziness; drowsiness; Depressed mood</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Epilepsy bipolar disorder</td>
<td>Potentially severe rash; severe blistering, peeling, chest pain; easy bruising or bleeding; nausea, stomach pain, increased liver enzymes, dizziness, drowsiness; blurred vision; nausea, vomiting, diarrhea, headache; weight loss; anxiety, insomnia, unusual dreams</td>
<td>Hypermobility</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormones</th>
<th></th>
<th>Smoking, prothrombophilias, venous thromboembolism, aura, diabetes, hypertension</th>
<th>Acne, menstrual-related migraine, PMDD, PMS, endometrosis, dysmenorrhea, dysfunctional uterine bleeding, polycystic ovarian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraceptive therapy</td>
<td>Contraception, dysmenorrhea, moderate acne (drospirenone &amp; ethinyl estradiol)</td>
<td>Bloating, irritability, depression, breast tenderness, sexual dysfunction</td>
<td>Vasomotor symptoms, night sweats, sleep disorders, osteoporosis, vaginal atrophy</td>
</tr>
<tr>
<td>Hormone replacement therapy (estradiol)</td>
<td>Menopausal symptoms</td>
<td>Bloating, irritability, depression, breast tenderness, sexual dysfunction</td>
<td>Smoking, prothrombophilias, venous thromboembolism, cholelithiasis, diabetes, hypertension, estrogen-dependent cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive Behavioral Therapy</th>
<th>Depression, anxiety disorders, psychiatric disorders</th>
<th>None</th>
<th>None</th>
</tr>
</thead>
</table>

GAD = general anxiety disorder; GI = gastrointestinal; LVD = left ventricular dysfunction; MAOI = monoamine oxidase inhibitor; MI = myocardial infarction; PMDD = premenstrual dysphoric disorder; PMS = premenstrual syndrome; PTSD = post-traumatic stress disorder.
Adverse Effects.—Common side effects include fatigue, decreased exercise tolerance, cold extremities, diarrhea, constipation, and dizziness. β-blockers can worsen or trigger depression. Vivid dreams, insomnia, impotence, and memory disturbances are also possible adverse events.26

Contraindications.—Contraindications include asthma, chronic obstructive pulmonary disease, diabetes, congestive heart failure, atrioventricular conduction defects, and peripheral vascular disease. Caution is advised for the combination of propranolol with duloxetine; via a 2D6 mechanism, this combination can produce elevated β-blockade with hypotension, bradycardia, and AV block.26

Calcium Channel Blockers.—Mechanism of Action.—Calcium channel antagonists block the
transmembrane influx of Ca2+ across cell membranes through slow, voltage-dependent channels. Several properties of these agents may mediate their effectiveness in migraine prophylaxis. Initially, it was thought that vasodilatory effects on cerebral vessels and inhibition of vasospasm were key mechanisms in their preventive role. However, nimodipine has little use in migraine prophylaxis and yet has vasodilatory properties on cerebral vessels. And one of the most effective calcium channel antagonists in migraine prevention, flunarazine (not available in the United States), exerts minimal effect on cerebral vessels in therapeutic doses, yet protects against excessive Ca2+ influx and release during cerebral ischemia. Flunarazine also inhibits synthesis and release of nitric oxide, a substance implicated in migraine pain. However, as the brain contains a high density of calcium channel binding sites – and evidence suggests that calcium channel antagonists affect neurotransmission – interaction with central nervous system (CNS) transmission may be the primary mechanism for their effectiveness in migraine.

When to Consider Calcium Channel Antagonists for Combination Therapy.—Calcium channel antagonists may be considered for polytherapy in migraineurs without contraindications to their use. They could be used in combination with antiepileptics (such as topiramate) or antidepressants (such as amitriptyline). Calcium channel antagonists may have a significant role in patients with hemiplegic migraine, a disorder associated with calcium channel mutations. As mitochondrial dysfunction has been implicated in migraine pathophysiology, vitamin B2 or CoEnzyme Q 10 may be effectively combined with a calcium channel antagonist in this subgroup of migraineurs.

Calcium channel antagonists could also be combined with low-dose aspirin for hemiplegic migraine or in RM with aura, as there is evidence that aspirin is an effective mild migraine preventive. In addition, aspirin has also been shown to decrease cerebrovascular and cardiovascular risks, which are increased in migraineurs with aura. One caution with this combination is that it may result in prolonged bleeding times.

Calcium channel antagonists could also be combined with magnesium, a supplement which can be useful in menstrual migraine as well as migraine with aura. In addition, as calcium channel blocker use is often associated with constipation, magnesium may help limit this adverse effect, as magnesium shortens gastrointestinal transit time, causing looser stools.

In RM patients with hypertension, calcium channel antagonists could be used in conjunction with another preventive such as an antiepileptic or antidepressant, with the final choice based on associated comorbidities and other medical problems.

**Adverse Effects.**—Common side effects include constipation, hypotension, atrioventricular block, edema, and nausea.

**Contraindications.**—Contraindications include bradycardia, second- and third-degree heart block, use of β-blockers, and sick sinus syndrome.

**Antidepressants.**—Only tricyclic antidepressants (TCAs) and dual serotonin norepinephrine reuptake inhibitors (SNRIs) have shown efficacy in migraine, although selective serotonin reuptake inhibitors (SSRIs) may be effective for headaches associated with premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD).

**Mechanism of Action.**—As with antihypertensives, multiple actions are responsible for the utility of antidepressants in migraine prophylaxis. The analgesic effect seems unrelated to their antidepressant action and is not attributed to inhibition of serotonin reuptake. TCAs also block alpha-adrenergic, histaminic, and muscarinic receptors. It is likely that their benefit involves effects on central pain pathways (via inhibition of serotonin and norepinephrine reuptake and attenuation of central sensitization via N-methyl-D-aspartate (NMDA) receptor agonism). Peripheral analgesic actions may also play a role. Noradrenergic agonist activity in the locus ceruleus is associated with gating attention to stimuli, including nociceptive stimuli; this may explain the relatively better performance in pain management of antidepressants that augment norepinephrine.

**Adverse Effects.**—Common side effects of TCAs include dry mouth, constipation, and sedation. They may also cause slowing of atrioventricular conduction and orthostatic hypotension. Common side effects of SSRIs and SNRIs include nausea, insomnia, and sexual dysfunction; dry mouth, constipation, and
sedation are less significant with these agents than with TCAs. Antidepressants, particularly the SSRIs, should be used with caution in bipolar disorder as they may unmask mania. In addition, antidepressants whether used as monotherapy or in combination with other agents that result in an increased availability of serotonin can precipitate the serotonin syndrome. While clinically relevant evidence of the serotonin syndrome is believed to be rare, the true prevalence of serotonin syndrome with antidepressants is unknown. And although a full review of the serotonin syndrome with use of serotonin modulating medications is beyond the scope of this article, it should be noted that in at least one small case series study, over 73% of patients diagnosed with serotonin syndrome presented within 24 hours of initiation, change, or overdosage of antidepressant medications.

When to Consider Antidepressants for Combination Therapy.—As depression, anxiety, and panic disorder are comorbid with migraine, antidepressants are a logical choice in their presence. In particular, a TCA such as amitriptyline or nortriptyline can be helpful in RM when weight loss is not desirable. These agents may be used in conjunction with an antiepileptic such as neurontin or valproic acid. Alternatively, in an obese depressed patient, protriptyline in conjunction with topiramate or zonisamide may be useful (Table 4). In this setting, antihypertensives such as verapamil and propranolol may be undesirable due to their potential for prolongation of the PR interval and QTc interval, respectively, as well as their potential for weight gain and decreased exercise tolerance. It should be noted, however, that TCA doses required for management of depression are greater than those needed for migraine prevention and may not be as well tolerated. TCAs may also be considered in migraineurs who suffer from fibromyalgia; in this setting, the combination of a TCA and gabapentin or pregabalin could benefit both disorders.

Although SSRIs are not effective for migraine prevention, they are indicated for PMS/PMDD. In migraineurs with these disorders, SSRIs are effective. If migraines are also present throughout the cycle, the combination of an SSRI with an antiepileptic or antihypertensive may be beneficial. Alternatively, venlafaxine is effective for both PMS/PMDD and migraine. It could be used alone or in combination with hormonal manipulation, antiepileptic medications, or calcium channel blockers for RM sufferers with PMS/PMDD.

Antiepileptics.—Topiramate and valproic acid are the only FDA-approved antiepileptics for migraine, although others have shown efficacy. Several relevant mechanisms of actions for antiepileptics in migraine prophylaxis have been demonstrated. Both topiramate and valproic acid block sodium channels, as do phenytoin, lamotrigine, carbamazepine, and oxcarbazepine. However, both topiramate and valproic acid also modulate gamma-aminobutyric acid (GABA), as do phenobarbital and gabapentin.

Adverse Effects.—For a complete review of adverse effects of antiepileptics, each drug should be reviewed individually in the Physician Desk Reference. Topiramate has been associated with sedation, cognitive dysfunction, paresthesias, weight loss, nephrolithiasis, and acute closed angle glaucoma. Valproic

<table>
<thead>
<tr>
<th>Drug class/drug</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>↑↑</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>↓</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>↓</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔/↓</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↔</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>↑</td>
</tr>
<tr>
<td>Topiramate</td>
<td>↓↓</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>↑</td>
</tr>
<tr>
<td>Serotonin (5HT) antagonists</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Methysergide</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>↑↑</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>↑↑</td>
</tr>
<tr>
<td>Flunarizine</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>↔</td>
</tr>
</tbody>
</table>

= weight increase; ↓ = weight decrease; ↔ = no effect on weight.
acid has been associated with encephalopathy, tremor, hair loss, weight gain, sedation, gastrointestinal symptoms, elevation of liver enzymes, hepatitis, agranulocytosis, and neural tube defects.\textsuperscript{52}

\textbf{When to Consider Antiepileptics for Use in Combination Therapy.}—Antiepileptics can be successfully combined with antidepressants to treat RM. Topiramate can be used in combination with a TCA or SNRI, antihypertensive or another antiepileptic. When obesity or diabetes complicates RM with depression, topiramate is an especially attractive candidate for polypharmacy with an antidepressant.\textsuperscript{46,52}

When nephrolithiasis complicates RM in a depressed obese patient, gabapentin or levetiracetam with an antidepressant such as venlafaxine or protriptyline may be considered.

Antiepileptics can also be utilized in RM with mood or personality disorders. Topiramate may not only be helpful for prevention of migraine in patients with bipolar or borderline personality disorder, but serve as adjunctive therapy of these psychiatric conditions.\textsuperscript{53,54} It could alternatively be combined with an antihypertensive (other than \(\beta\)-blockers which may augment depression), another antiepileptic or lithium in these settings. Similarly, gabapentin may also be used with an antihypertensive (other than \(\beta\)-blockers), or another antiepileptic in a RM patient with bipolar disorder.\textsuperscript{55} Finally, the use of lamotrigine in combination with another antiepileptic, an antidepressant, an antihypertensive, or magnesium could be considered in a migraineur with frequent or status aura.\textsuperscript{38,39,56}

\textbf{Hormonal Manipulation.}—Sex hormones can have significant impact on migraine throughout a woman’s life. There are multiple potential indications for use of hormones in combination with another pharmacological agent. In particular, for the woman who requires contraception or hormone replacement, who has acne, PMS/PMDD, or certain gynecological disorders such as endometriosis or dysmenorrhea, the use of hormonal agents in conjunction with another preventative should be considered.\textsuperscript{42,57-59}

\textbf{Hormonal Contraceptives.}—WHEN TO CONSIDER HORMONES FOR COMBINATION THERAPY WITH OTHER PROPHYLACTICS. —In women with menstrual-related migraine (MRM) who require contraception, the use of extended cycle contraceptives should be considered in combination with other preventives.\textsuperscript{50,60} Examples include commercially available extended cycle 30 \(\mu\)g ethinyl estradiol (EE) products combined with levonorgestrel; alternatively, traditional 30 \(\mu\)g EE products with other progestins can be used in extended regimens by eliminating the placebo week for months at a time. This would also represent logical polypharmacy in RM complicated by endometriosis or dysmenorrhea as hormonal contraceptives have FDA indications beyond contraception — including endometriosis, dysmenorrhea, dysfunctional uterine bleeding, polycystic ovarian syndrome, and acne.\textsuperscript{61} Hormonal contraceptives have also been advocated for women at high risk for endometrial cancer or ovarian cancer, as substantial reductions in these malignancies have been attributed to long-term use of oral contraceptives (OCs).\textsuperscript{52,53}

When using OCs in combination with antiepileptics, it is important to be aware of significant interactions. Doses of topiramate over 200 mg are reported to interfere with the efficacy of OCs. It is of note, however, that efficacy of OCs is primarily attributed to the progestin component, and none of the antiepileptic drugs (AEDs) commonly used for migraine prevention (topiramate, valproic acid, gabapentin, levetiracetam) decrease progestin concentration. However, the increased rate of metabolism of estrogen in the presence of topiramate can lead to daily instability of estrogen concentration with potential adverse effect on migraine.\textsuperscript{64} Use of topiramate might argue for changing an OC to a patch or ring formulation, thereby avoiding the first-pass effect through hepatic circulation.\textsuperscript{65} Use of an estrogen containing OC significantly decreases lamotrigine plasma concentrations, often necessitating higher doses of that drug.\textsuperscript{66}

\textbf{ADVERSE EVENTS.}—Adverse events include bloating, irritability, depression, breast tenderness, and sexual dysfunction.\textsuperscript{49} Most of these effects are attributed to the progestin component and can be addressed by switching to a different progestin or to a lower progestin concentration. More serious adverse events are rare but include venous thrombosis, pulmonary embolism, stroke, and myocardial infarc-
tion.67 Cardiovascular events are minimized with the lowest-dose contraceptives and proper patient selection. Contraceptives with androgenic progestins (such as norethindrone) can cause lipid abnormalities and acne.67 However, non-androgenic progestins such as desogestrel have a more favorable lipid profile and may be used as more rational co-therapy in women with lipid abnormalities; contraceptives containing norgestimate or drospirenone are indicated for treatment of acne vulgaris.68 Although weight gain has been seen with some OCs, many are weight neutral, and drospirenone-containing contraceptives are even associated with mild weight loss, making them a reasonable choice for obese patients.69 Caution is advised when combining drospirenone-containing OCs with angiotensin converting enzyme (ACE) inhibitors for migraine prevention, since this combination could result in hyperkalemia.69

CONTRAINDICATIONS.— Contraindications include smoking (especially over the age of 35), diabetes, hypertension, inherited prothrombophilias (such as Factor V Leyden), venous thromboembolism, and presence of aura.69,70 Even though MRM is rarely associated with aura, some women with MRM may still experience aura at other times of the cycle. Higher concentrations of estrogen are associated with an increased incidence of aura, so in RM patients with MRM and occasional aura, use of the ultra-low-dose ring contraceptive may be a reasonable option.71 Similar to the 30 or 35 μg OCs, these products often prevent ovulation. However, unlike the pills, the much lower concentration of estrogen in the ring – in the setting of anovulation – results in a lower peak exposure to estrogen throughout the month than the native menstrual cycle. The ring is particularly effective at preventing ovulation when used in extended cycle dosing.72

MECHANISM OF ACTION.—Combined hormonal contraceptives prevent conception by three mechanisms, all of which are attributed to the progestin component. The efficacy of extended cycle hormonal contraceptives in migraine is thought to be mediated by one of these mechanisms: inhibition of ovulation. With prolonged inhibition of ovulation, women experience relative stability of estrogen content due to anovulation combined with the stable EE content of the contraceptive. Today’s low-dose OCs, however, do not always inhibit ovulation when used in the traditional 21/7 regimens (which allow for a 7-day placebo week following 21 days of active pills).73,74

Hormone Therapy (HT).—Postmenopausal HT utilizes different hormones in different dose ranges from those in contraceptives; they have attendant differences in indications, adverse events, and mechanism. Whereas the estrogen used in contraceptives is always a synthetic estrogen (usually EE, but rarely mestranol), the estrogen in HT is more often a natural estrogen (bioidentical, conjugated, or esterified). Whereas most contraceptives utilize supraphysiologic doses, most HT is in physiologic or subphysiologic dose ranges.

WHEN TO CONSIDER ADDING HT TO MIGRAINE PREVENTATIVES.—Perimenopausal or menopausal women with RM who experience significant vasomotor symptoms may be good candidates for addition of HT to their migraine preventive. Sleep problems often dominate perimenopausal symptoms and include night sweats and sleep fragmentation, both of which have been shown to respond to HT. A 5-fold increase in sleep apnea (both central and obstructive) has been reported to occur in perimenopause, but was not seen in current users of HT.75 It is important to remember when considering co-therapies that HT is also indicated for prevention of postmenopausal osteoporosis and for treatment of vulvovaginal atrophy.76

ADVERSE EVENTS.—Although recent studies have confused this issue by studying the initiation of HT in women a decade or more beyond menopause, certain risks are undoubtedly associated with HT. They include, most prominently, an increased risk of venous thrombotic events (HT more than doubles the risk, although absolute numbers remain low) and cholecystitis.77 Two studies showed that cardiovascular events are more common in the first year after initiation of HT (possibly mediated by inherited prothrombophilias).78,79 while a larger longitudinal study suggests primary prevention of cardiac disease when HT is begun in perimenopause.80 The Women’s Health Initiative reported a significant 27% increased risk of breast cancer diagnosis within 5 years follow-
ing initiation of combined (estrogen plus progestin) HT and an insignificant 23% decreased risk with estrogen alone.\textsuperscript{81}

CONTRAINDICATIONS. — Contraindications include venous thromboembolism and presence of an estrogen-dependent cancer.\textsuperscript{82}

Cognitive Behavioral Therapy. — Cognitive behavioral therapy should be strongly considered in RM patients as well as in migraineurs with a history of depression, abuse, post-traumatic stress disorder, or other psychiatric disorder. Behavioral therapy in addition to pharmacological intervention may be more effective than either treatment alone.\textsuperscript{83} An in-depth discussion of behavioral therapy is presented in a separate article in this supplement.

Greater Occipital Nerve Blocks (GONB) and Botulinum Toxin. — GON fibers arise from the dorsal root of C2; and both the trigeminal afferents and the first 2 upper cervical nerve afferents converge upon the trigeminal nucleus caudalis, possibly explaining why GONB decrease head pain and allodynia.\textsuperscript{84,85} In one study, GONB were shown to decrease the total pain index by 50% or more in 23 of 27 patients who had previously failed several combinations of pharmacological treatment.\textsuperscript{85} Afridi et al showed significant response to GONB in both migraine and cluster headache with minimal side effects.\textsuperscript{23} However, it should be noted that Afridi et al also demonstrated that the mean duration of complete response was 20 days, with a median of 7 days. Similarly, the mean duration of partial response was 45 days with a median of 20 days for GONB. Thus, the benefit in RM could be limited by the need for repetitive injections. In RM patients who do not wish to add additional oral medications to their regimen, GONB may be a viable option and may help to limit adverse effects from drug interactions. Adverse events include injection site reactions, alopecia at the injection site, dizziness, and vasovagal syncope.\textsuperscript{23,84,85}

As with GONB, botulinum toxin has evidence of benefit for RM and is an option for those who are hesitant to add additional medications or seek to limit the potential for drug–drug interactions. Side effects include injection site reactions, ptosis, and lacrimation.\textsuperscript{21,86-88}

LENGTH OF PREVENTIVE TREATMENT UTILIZATION

Data guiding duration of preventive therapy are limited, although 2 studies have addressed the topic. In the first, Wober et al followed 64 migraineurs after discontinuation of successful prophylaxis used up to 6 months.\textsuperscript{89} Following discontinuation of preventive medication, 75% of patients experienced a relapse in migraine, and further attempts at prophylaxis, utilizing the same agents, were less successful than the first.

More recently, Pascual et al evaluated 80 migraineurs who received preventive treatment with topiramate.\textsuperscript{90} After 6 months the preventive was stopped. Topiramate was reintroduced for 6 additional months if the subject worsened, then again discontinued. Following the second withdrawal, patients whose headaches again worsened received a third round of topiramate and were followed up for at least half a year. After the first withdrawal, headaches worsened in 50% of patients. In these patients only 5% were able to stop topiramate without an increase in headache frequency within 2 months. The authors suggested that the current practice recommendation of 3-6 months of preventive treatment may be inadequate for many patients. Based on these studies we suggest preventative therapy be continued for at least one year.

CONCLUSION

Migraine extracts a substantial personal and societal burden. Although it is unknown if migraine preventative therapy confers disease modification, preventive therapy is frequently associated with pain relief and reduction in disability. Limited data and clinical experience suggest that combination therapy should be considered in migraineurs who present with disability and a history of repetitive failed preventive regimens in the past (ie, RM). Although there are very few controlled trials, combination therapy may also be beneficial for migraineurs with comorbid disorders, medication-overuse headache, early onset, and strong family history.

Clinically, headache specialists have used rational combination therapy to treat RM for years. In this article we reviewed several logical combinations of medications for migraine prevention in refractory migraineurs. Many other combinations and rationales...
for polytherapy exist. Based on the extreme paucity of data in regards to combination therapy and RM, extensive research is sorely needed to guide treatment of this special subpopulation of migraineurs. One possible way this could be accomplished is for randomized double-blind studies to be undertaken to evaluate participants who are all on one standard preventative medication (similar to Pascual et al’s open-label study), and in one arm of the study participants add a second migraine preventative, whether it is a traditional migraine preventative, a supplement, a form of hormonal manipulation, or a behavioral intervention (R.B. Lipton, verbal communication). Studies such as these will help allow the development of evidence-based medicine in RM treatment, and ultimately and hopefully, provide effective treatment options for safe and faster relief to refractory migraineurs.

REFERENCES


