Managing Menstrual Migraine

How to Avoid That Monthly Misery

Migraine is roughly 3 times more common in females than males, and the female preponderance is most obvious between ages 15 and 45. While this epidemiologic gender imbalance conceivably may be multifactorial, it seems inescapably obvious that the greater and more complex fluctuation in sex hormone levels - estrogen in particular - that occurs in females plays a major if not solo role.

Roughly 2/3rds of actively cycling female migraineurs experience menstrual aggravation of their headache disorder. While a small proportion of these females have "pure" menstrual migraine, with migraine episodes occurring only in association with menses, most have migraine symptoms at other times of the month as well.

Many females with menstrually-associated migraine (MAM) report that the migraine episodes that occur with menses are different from those that occur at other times of the month. Data collected from systematic surveys have indicated that for many females the headache of MAM is more severe, longer in duration and more difficult to treat. For many women with MAM, migraine episodes associated with menses are characterized by one uninterrupted headache that rolls along for days (status migrainosus) and stubbornly refuses to respond to whatever treatment is thrown its way. As will be discussed shortly, when one is designing a strategy for treating MAM, it's helpful to keep these factors in mind.

In the subgroup of those individuals who have migraine with aura, aura is less likely to occur with a menstrual migraine episode. In fact, the latest edition of the International Classification of Headache Disorders (ICHD-3) includes diagnostic criteria only for "pure menstrual migraine without aura" and "menstrually related migraine without aura". The ICHD-3 criteria mandate that migraine attacks must occur within the 2 days preceding flow onset, on the day of flow onset and/or the 2 days following flow onset. In reality, many women who clearly have MAM report aura accompanying their headaches and experience cyclical headaches that may fall up to a day or so outside this "official" range.

When we assess migraine burden in new patients presenting to our clinic, it is often remarkable how much of that burden resides squarely within the menstrual week. So how can we help those patients reduce the disproportionately onerous burden of menstrual migraine?

Acute Treatment

In the phase 3 clinical trials that earned each drug its FDA indication for acute migraine treatment, all of the triptans, ubrogepant (*Ubrelvy*), rimigepant (*Nurtec*) and lasmiditan (*Reyvow*) appeared to work just as well for episodes of menstrual migraine as for they did for migraine occurring at other times of the month. In the "real world", however, many women find that the acute therapy that typically works quite well at other times is less effective or even ineffective for their MAM. Even so, these medications deserve a chance, and using them appropriately may improve their performance.

For example, if your MAM episodes are typically prolonged, lasting for days, keep that fact in mind as you choose and administer your therapies. If on the day of flow onset you awaken with a severe migraine headache that is clinically and biologically well-developed, it is highly unlikely that any oral medication will make much of a dent. There is a "need for speed"

in such circumstances, and unless you have a cardiovascular disorder or another medical condition that contraindicates use of the drug or you have not had a good experience with it in the past, your best bet is injectable/subcutaneously self-administered sumatriptan. Nothing else you can administer is going to give you such a high blood level of a "designer drug" for migraine so rapidly.

Remember, however, that the half-life* of this drug in your body is no more than an hour or two, and within a short time it will have left the building [*the amount of time required for the blood concentration of the drug to drop by 50%]. Anticipate this. Unless you were lucky enough to have nailed the migraine completely and shut down all activity on the migraine circuitry, the circuitry will reactivate, and the headache will recur. Be ready. As the headache begins to build, immediately administer whatever oral medication you have found to be effective in the past. While my favorite choice in this setting is an oral triptan combined with a nonsteroidal anti-inflammatory drug (NSAD) such as naproxen sodium, either Nurtec, Ubrelvy, or Reyvow is an entirely suitable alternative. If you choose 1 of the 5 "fast onset" oral triptans, recall that their tenure in your body is only a few short hours just as with injectable sumatriptan; you may experience re-emergence of your headache when the oral triptan has gone on its way. The "slow onset" oral triptans (naratriptan/*Amerge* and frovatriptan/*Frova*) hang around longer, but the downside is that they may be slower in providing headache relief.

If your acute headache is not mind-bendingly severe, one of the nasal sprays may serve as an adequate substitute for injectable sumatriptan. Zolmitriptan (*Zomig*) administered by nasal spray has an onset of action faster than the oral triptans but slower than injectable sumatriptan, and it has a short half-life (3 hours), so as with injectable sumatriptan anticipate early recurrent headache. The dihydroergotamine (DHE) nasal spray (*Trudhesa*) also gets on board quickly, and it's relatively long half-life (12 hours) may render it an especially appropriate treatment for MAM that typically presents as status migrainosus. One potentially complicating factor: use of Trudhesa and a triptan within 24 hours of one another theoretically carries a risk of provoking constriction of blood vessels, with myocardial infarction (heart attack) or another vascular complication.

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"Mini-prophylaxis"

Especially given MAM's tendency to shrug off attempts at acute treatment, an alternative and complementary approach to acute treatment involves attempting to stop the MAM attack before it starts. While all of the treatments to be described here are "off-label" and do not possess much in the way of a true evidence base beyond published case reports and case series, most have at least passed the test of time: they have been prescribed for many patients by many providers, appear to be safe and for many migraineurs seem to be effective.

Caveats

1. While care obviously should be taken to avoid any adverse drug-drug interactions, it often is more effective to use multiple complementary therapies for mini-prophylaxis rather than a single treatment.

> **An alternative approach to acute treatment involves stopping menstrual migraine before it starts**

2. Mini-prophylaxis appears to be more effective if treatment is started a day or two before the you begin to have your MAM, rather than after the MAM already has started (a management strategy that admittedly may be impractical unless your cycles are regular, you can accurately predict the day of flow onset and you consistently have experienced headache onset at more or less the same point in relative to flow onset).
3. If you have a breakthrough headache despite your mini-prophylaxis, treat that headache aggressively with appropriate medication.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Try scheduled use of an NSAID such as naproxen sodium twice daily or ibuprofen 3 times daily. Start the treatment a day or 2 before anticipated onset of MAM and continue treatment for 5 to 7 days.

Oral triptans

Similar scheduled use of an oral triptan has been studied and found to be helpful for some patients. Recall that biologic half-lives vary widely amongst the oral triptans, with Frova having (at 26 hours) by far the longest half-life within the group… roughly 5 times that of the next longest (Amerge). If you choose a "fast-onset"/short duration half-life oral triptan such as sumatriptan or rizatriptan for mini-prophylaxis, taking the drug three times daily makes pharmacokinetic sense.

Of the oral triptans, Frova has been by far the most carefully studied as a therapy for MAM mini-prophylaxis. In 1 well-conducted study of females with difficult to treat MAM, Frova 2.5 milligrams taken once or twice daily, started two days prior to predicted MAM onset and continued for 6 days was safe and effective in reducing days with migraine.

Rimigepant (Nurtec)

As was discussed in a previous issue of this magazine, Nurtec is a "hybrid" migraine medication which is FDA-indicated both for acute migraine treatment and for migraine prevention. Amongst the oral triptans, only Frova has a longer biologic half-life than Nurtec. This relatively long half-life, its high tolerability and its rapid onset of action make Nurtec a logical choice for mini-prophylaxis of MAM.

While there currently do not exist any meaningful data regarding Nurtec's safety and effectiveness in the treatment of MAM, in our clinic we typically prescribe 75 mg daily during the "high risk" time (beginning treatment a day or two before anticipated onset of MAM and continuing treatment for 5 to 7 days).

Aside from the lack of an evidence base, at this point the greatest roadblock to using Nurtec routinely for MAM mini-prophylaxis is the patients' understandable reluctance to use up all or most of their monthly supply during the menstrual week…leaving little or none for treating migraine episodes that occur at other times of the month.

Magnesium

When used for mini-prophylaxis of MAM, magnesium started up to 15 days prior to onset of menses has been found to be safe and effective. Virtually any preparation of magnesium will suffice, but magnesium oxide and magnesium citrate are easily found and the most commonly used. The recommended dose is 400 milligrams taken once or twice daily. The most common side effects are gastrointestinal (diarrhea, nausea); if they occur and are bothersome, try a different preparation.

Hormones

Blunting the natural monthly drop in estrogen levels that appears to be the primary trigger of MAM may be effective for some individuals. This can be accomplished through estrogen supplementation via a pill, patch or vaginal gel used during the menstrual week. Especially in individuals taking an estrogen-based oral contraceptive pill (OCP), using a pill with lowest possible estrogen concentration and thus minimizing the degree of drop in estrogen levels during the pill-free week may have a positive effect on MAM.

A somewhat more aggressive hormonal approach involves eliminating menses through use of an active estrogen-based OCP throughout the month, continuous use of a vaginal ring or use of a hormone-secreting IUD.

Other

Many individuals with MAM already are taking medication for migraine prophylaxis throughout the month, and some headache subspecialists have recommended transiently increasing the dose of the patient's usual prophylactic medication during the high risk week. At least on a theoretical basis, an excellent choice for such treatment management is atogepant (Qulipta). Qulipta is FDA-approved for the prevention/suppression of both episodic and chronic migraine, and clinical research trials and from experience in clinical practice the medication is often rapidly effective. If you are taking the 30 milligram formulation of Qulipta during the rest of the month, increasing your dose to 60 milligrams daily during the high-risk week theoretically may be helpful in preventing MAM. Whether it would be useful taken for mini-prophylaxis only during the menstrual week (like the other medications discussed previously) is unknown but, again, theoretically possible.

Summing Up

For the female population, the World Health Organization ranks migraine number one amongst the chronic medical disorders that negatively impact quality of life. The majority of actively cycling females experience menstrual aggravation of their migraine. It follows that MAM represents a major public health problem…and one deserving of effective treatment. If *you* have MAM, some or all of the therapeutic options described here may help you minimize your menstrual migraine.