Rational Polypharmacy for Migraine

Polypharmacy can be effective for migraine refractory to monotherapy.

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Migraine is a complex and debilitating neurologic disease ranking second in causes of years lived with disability worldwide.[1] A multitude of evidence-based preventive and acute therapies from different pharmacologic classes are available for treatment, with the recent emergence of calcitonin gene-related peptide (CGRP) blocking agents revolutionizing the field. Despite these developments, a substantial number of individuals have migraine attacks that are intractable or refractory to treatment, making migraine management a continued challenge. For individuals with migraine refractory to monotherapy, polytherapy may be prudent to carefully consider as part of the treatment regimen.

Advantages and Disadvantages of Polypharmacy

Monotherapy is a priority when managing migraine because it simplifies the treatment plan and decreases likelihood of potential adverse effects and drug interactions.[2] Monotherapy also makes adherence to therapy more attainable and diminishes cost. Unfortunately, in clinical practice, less than 50% of persons with migraine have at least a 50% reduction in attack frequency with prophylaxis.[3] When considering acute treatment, a single agent may not provide rapid, dependable, and complete relief. Approximately 30% of people prescribed a serotonin receptor (5-$HT_{1B/1D}$) agonist discontinue use due to lack of efficacy, attack recurrence, or side effects.[4] Among the newer medications, approximately 40% of individuals require a second dose, and 15% needed a rescue medication after being treated with ubrogepant.[5] For those who discontinue serotonin-receptor agonists for these reasons or need multiple doses of CGRP receptor antagonists (ie, gepants), polytherapy may play a role because it may promote a synergistic effect by acting on different pathophysiologic mechanisms involved in migraine.

Polytherapy may lead to better outcomes and allow for lower dosages than are used traditionally but does come with disadvantages that should be cautiously considered (Figure). Using multiple agents increases the potential for adverse events and can make it difficult to determine which treatment is causing an adverse effect. Polytherapy also increases the likelihood that an individual will discontinue medication on their own due to side effects or a complicated regimen.[6] The paucity of evidence for polypharmacy may also lead to reluctance. There are few validated studies supporting polypharmacy and these have small sample sizes, assess different medication combinations, and include therapies that are not considered first- or second-line treatment.[3] These disadvantages do not preclude the use of polypharmacy, however, which may be a logical choice for select individuals.

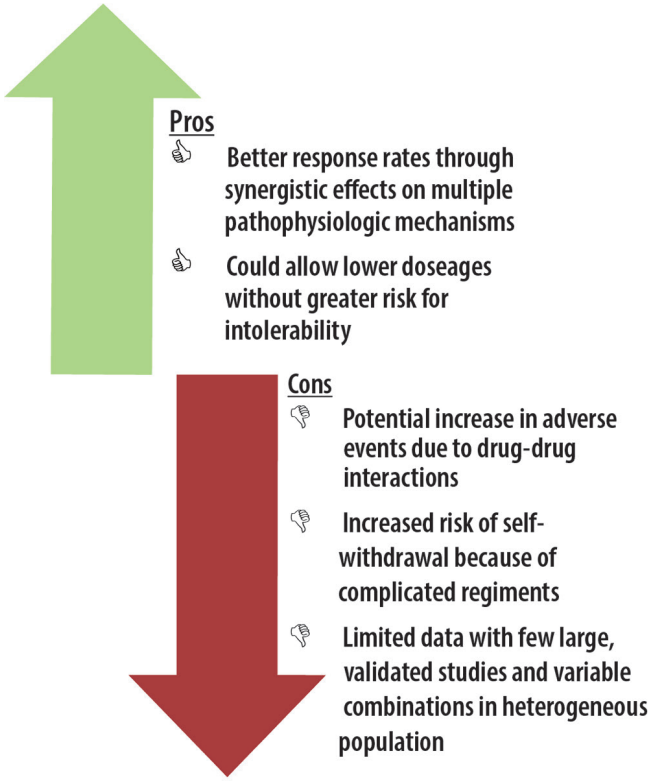

Figure. Advantages vs disadvantages of using polypharmacy in migraine management.

Polypharmacy in Acute Migraine Treatment

When considering who may benefit from polytherapy, it is beneficial to review the goals of acute migraine treatment. The 2021 American Headache Society consensus statement on integration of new migraine treatments into clinical practice states that an acute therapeutic should achieve 1) rapid and consistent freedom from pain and associated symptoms without recurrence, 2) restored ability to function, 3) minimal need for repeat dosing or rescue medications, 4) optimal self-care and reduced subsequent use of resources, and 5) minimal or no adverse effects.[7] Effective acute treatments are crucial because they not only treat attacks in real time but also help prevent disease progression (worsening of attack severity or increased frequency of attacks).[8] Consequently, if monotherapy results in suboptimal relief, polytherapy targeting different physiologic mechanisms should be considered.

During migraine attacks, meningeal vasodilation leads to the activation of trigeminovascular afferents, resulting in C-fiber meningeal nociceptor activation, CGRP release, and neurogenic inflammation.[4] The 5-$HT_{1B/1D}$ agonists (ie, triptans and dihydroergotamine [DHE]), CGRP-receptor antagonists (ie, gepants), and 5-HT_{1F} agonists (ie, ditans) specifically target these mechanisms and have positively impacted clinical practice for many. None of these agents, however, provide complete, consistent, and sustained relief for all treated individuals.[4,5,7,9] In addition, once central and peripheral sensitization has occurred, these acute therapies are not as effective.[4,9,10]

Nonspecific, anti-inflammatory agents reduce pain severity and decrease neurogenic inflammation in the trigeminal ganglion, preventing central sensitization[4,9] which can allow serotonin-receptor agonists and CGRP-receptor antagonists to exert their effects more efficiently. Such synergy is evident in the greater pain relief and lower recurrence rates demonstrated across multiple studies of combination therapy (Table 1). In a randomized, double-blind, placebo-controlled, multicenter study in 965 participants, sumatriptan and naproxen used together provided a sustained pain response in 46% of those treated vs approximately 25% of those treated with either agent alone.[11] It may also be advantageous to consider using dopaminergic antagonists to treat migraine attack symptoms (eg, headache, nausea, hypotension, and yawning) as well as to promote gastric motility and increased gastric absorption of subsequent medications.[4,9] Before the development of triptans, a study showed 61% of individuals had complete or significant relief with a combination of a dopamine antagonist and simple analgesic; this increased to 91% with the addition of an ergot preparation. An effective emergency room protocol combining intravenous (IV) prochlorperazine and dihydroergotamine (DHE) has also been developed.[4,9]

The safety profiles of the aforementioned combinations are low risk; however, triptans and DHE are 2 classes of medications that should not be used within 24 hours of each other because of the theoretical risk of vasospasm with combined use. Considering triptans are potentially harmful to patients with underlying coronary artery and cerebrovascular disease, additional agonistic activity by DHE at the 5-HT_1 receptors could lead to dire consequences.[12] There is also considerable interest in the combination of ditans with triptans or CGRP receptor antagonists, but the safety and efficacy of these combinations have not yet been studied.[7]

TABLE 1. CURRENT & POTENTIAL POLYPHARMACY FOR ACUTE MIGRAINE TREATMENT

Combination	Examples	Level of Evidence
Triptan + NSAID	Rizatriptan + rofecoxib; sumatriptan + naproxen	Few small studies with different combinations and heterogeneous populations showed sustained pain response at 2 and 24 hours is higher with the combination vs monotherapy[11]
Simple analgesic + dopaminergic antagonist	Aspirin + metoclopramide	A >50% reduction in pain was noted with this combination in 1 study[4,9]
DHE + dopamine antagonist	Metoclopramide + DHE	Combination allowed faster gastric absorption of DHE[4,9]
Gepant + NSAID/simple analgesic	Ubrogepant + acetaminophen	Phase 1 studies showed nonsignificant pharmacokinetic interactions[12-14]
Triptan + gepant	Ubrogepant or rimegepant + sumatriptan	Phase 1 studies showed nonsignificant pharmacokinetic interactions[12-14]
DHE + triptan	Contraindicated in combination or within 24 hours of each other due to risk of vasospasm[12]	
DHE or ditan + NSAID	No studies to date; may be appropriate due to differing mechanisms (5-HT vs COX inhibition)	
DHE or ditan + gepant	No studies to date; may be appropriate due to differing mechanisms (5-HT vs CGRP inhibition)	
Ditan + triptan or DHE	No studies to date, although there is a concern for serotonin syndrome	

Note: Triptans are 5-$HT_{1B/1D}$ receptor agonists, gepants are CGRP antagonists, and ditans are 5-HT_{1F} receptor agonists.
Abbreviations: 5-HT, serotonin; CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; DHE, dihydroergotamine; NSAID, nonsteroidal anti-inflammatory drug.

Coadministration of the CGRP-receptor antagonists with other classes of medications is an area of growing interest, with pharmacokinetic interactions investigated in phase 1 studies. A combination of ubrogepant and acetaminophen resulted in a 40% increase in the peak serum concentration of ubrogepant while decreasing the peak serum concentration of acetaminophen by 24%.[13] In contrast, combining sumatriptan with ubrogepant doubled the median time to maximum plasma concentration of ubrogepant (from 1.5 to 3 hours), and reduced the mean maximum plasma concentration of ubrogepant by 24%.[14] Coadministration of rimegepant and sumatriptan resulted in a minimally higher (<30%) reduction in peak serum concentration of rimegepant.[15] No significant pharmacokinetic interactions were noted with either of these combinations. Although these changes were described as not being clinically relevant, further studies are required to determine if these are viable treatment options.

It is important to remember that not all migraine attacks are equal and individualizing and combining treatments may be necessary. Using a stratified treatment approach, individuals can select and combine therapies based on intensity and associated features of particular migraine attacks. For example, an individual may find that mild to moderately severe attacks or those associated with cervicogenic pain may be more responsive to anti-inflammatory agents, whereas more severe attacks may be more responsive to a migraine-specific therapy. Similarly, sudden-onset attacks may be more responsive and adequately treated with subcutaneous options that bypass gastrointestinal absorption, and attacks associated with significant nausea and/or vomiting may benefit from nasal administration or oral-disintegrating formulations.

Providers should consider self-administered rescue options for those who have a history of nonresponsiveness to acute medications. Options include oral valproic acid or steroids and subcutaneous sumatriptan, intranasal or intramuscular DHE, or intramuscular ketorolac.[7] Neuromodulation devices may also be ideal for individuals who prefer nonpharmacologic options or for those who have frequent attacks and are at risk for medication-overuse headache. Neuromodulation devices can also work for those with contraindications or inability to tolerate acute therapies.[16]

Polypharmacy in Preventive Migraine Treatment

Traditionally, the recommendation has been to use a single agent to treat migraine and concomitant conditions when possible. Although this approach simplifies management, reduces polypharmacy, and minimizes side effects, it may also result in suboptimal treatment of either condition because of dose variations, treatment timelines, or poor tolerability with coexisting diseases. Consideration of therapeutic independence, which involves treating each comorbid condition separately, takes precedence.[17]

Simultaneous individual treatment of comorbid conditions is separate from true polytherapy in the preventive management of migraine. Whenever possible, single agents should be used, especially with the advent of the newer migraine-specific therapies. Because approximately 40% of individuals do not significantly benefit from monotherapy for migraine prevention, however, using multiple agents from at least 2 different preventive medication classes may be beneficial.[18] Although therapeutic independence should be prioritized, utilizing medications that confer positive benefits for coexisting conditions may still prove to be beneficial. Although small in sample size, multiple studies show that individuals whose migraine attack frequency is not reduced by a single agent may have an equal or greater response with polypharmacy, even at lower doses, with few tolerability issues (Table 2).

In 2 open-label studies, individuals whose migraine attacks did not respond to monotherapy with β-blockers or antiseizure medications (ASMs) had better results when these were used in combination. When treated with such a combination, a greater than 50% reduction in headache frequency was noted in 56% of treated with propranolol and divalproex sodium[19] and 62% treated with propranolol and topiramate.[20] Propranolol was also found to be well tolerated when combined with nortriptyline,[21] although caution should be used when combined with duloxetine because of the resulting increased β-blockade.[18] β-blockers may be considered in those who have had an inadequate response to ASMs or antidepressants, especially in those who also have hypertension or performance anxiety.

ASMs (eg, topiramate or gabapentin) can influence GABA and glutamate receptors to act on cortical hyperexcitability and tricyclic antidepressants (TCAs) influence central serotonergic and noradrenergic systems. Combining these agents is appealing because of effects on multiple physiologic processes of migraine and because the common side effect of weight gain with tricyclic antidepressants can be counteracted by simultaneous use of topiramate.[22] In a randomized, controlled study the combination of topiramate and nortriptyline resulted in a greater than 50% reduction of headache frequency in 78% of those treated compared with 37% treated with monotherapy.[23] In another double-blind randomized controlled trial, polytherapy with topiramate and amitriptyline was not superior to monotherapy for reducing migraine attack frequency but did lead to higher patient satisfaction.[24] Topiramate may enhance the central nervous system (CNS) depressant effect and serum concentrations of TCAs. Conversely, TCAs may enhance the adverse effects of topiramate; monitoring for hypohidrosis and hyperthermia during physical activity is warranted.[25]

There is a great deal of interest in concomitant use of onabotulinumtoxinA and monoclonal antibody (MAb) treatments (ie, erenumab, eptinezumab, freman-

TABLE 2. CURRENT AND POTENTIAL POLYPHARMACY FOR PREVENTIVE MIGRAINE TREATMENT

Combination	Examples	Level of Evidence
β-blocker + ASM	Propranolol + divalproex sodium; propranolol + topiramate	Few small studies with different combinations have shown a > 50% reduction in headache frequency as compared to monotherapy[17-18]
β-blocker + TCA	Propranolol + nortriptyline	A small randomized controlled trial showed that the combination did not result in higher intolerance or more frequent side effects[19]
ASM + TCA	Topiramate + amitriptyline or nortriptyline	A small randomized controlled trial showed a > 50% reduction in headache frequency with dual vs monotherapy[21] and another showed no significant difference in frequency, but dual therapy resulted in higher patient satisfaction[22]
CGRP Mab + onabotulinumtoxinA	Erenumab + onabotulinumtoxinA	Multiple small studies have shown a greater reduction in mean headache/migraine days with combination[26-27]
CGRP Mab + gepants	Galcanezumab + rimegepant;	Small studies with combinations were well tolerated with no increase in adverse effects[31,32]
CGRP Mab + oral migraine preventive medication	Erenumab + topiramate; fremanezumab + propranolol	Post-hoc analysis of 2 randomized placebo-controlled studies showed a greater decrease in monthly migraine days, mean monthly days with moderate-severe headaches, and mean days with acute medication use.[29-31]
Behavioral therapy + oral migraine preventive	Behavioral management + propranolol; biofeedback + flunarizine	Few studies have shown that combination improved outcomes of optimized acute treatment more so than monotherapy[32] and leads to superior long-term management of migraine with analgesic overuse[33]
Neuromodulation + oral migraine preventive	No studies to date, but given different mechanisms combination would be a great option in those who prefer non-pharmacologic options or are unable to tolerate higher doses	

Abbreviations: ASM, antiseizure medication, CGRP, calcitonin gene-related peptide; MAb, monoclonal antibody; TCA, tricyclic antidepressant.

ezumab, and galcanezumab), which block CGRP activity. Preclinical data suggests there may be a synergistic effect resulting from the distinct mechanisms of these agents. OnabotulinumtoxinA blocks the fusion of synaptic vesicles thereby inhibiting CGRP release from unmyelinated C fibers and dural nociceptor activation. The CGRP-targeted MAbs, in contrast, prevent trigeminal activity and CGRP activation on thinly myelinated Aδ fibers.[26,27] Multiple retrospective and prospective studies show more reduction in the mean headache or migraine days with this combination,[28,29] with a study suggesting that the MAbs may be an effective add-on for those who experience a "wear-off" phenomenon with onabotulinumtoxinA.[30] Constipation is the most commonly noted adverse effect of the MAbs, and more people in these studies chose to discontinue MAbs vs onabotulinumtoxinA.[28] Although no additional safety concerns emerged with the combination, there is a theoretical concern that excess CGRP antagonism could lead to more local adverse effects, including impaired tissue repair, wound healing, and dermatitis, which should be monitored.[28]

The combination of the CGRP-targeted MAbs with gepants is garnering increased attention and controversy. Both classes are effective with relatively few side effects. Because the MAbs act peripherally, whereas gepants cross the blood-brain barrier and act centrally, it is proposed that dual use might lead to greater efficacy. The concern exists, however, that because both classes block CGRP activity, the combination might be redundant without any additional therapeutic effect, or conversely, cause too much inhibition of the CGRP pathway increasing adverse effects. There are 2 small studies suggesting combination of these therapies may be complementary, but further investigation in larger populations is needed to support these findings.[31,32]

Beyond onabotulinumtoxinA, the antiCGRP MAbs also have favorable effects when combined with oral preventive migraine treatments.[33,34] Post hoc analysis of 2 randomized placebo-controlled studies in people with episodic and chronic migraine (n=133) on stable preventive medications with added fremanezumab treatment vs placebo had decreases in monthly migraine days (-4.12 vs -2.47, *P*=.032), mean monthly days with moderate-to-severe headache (-4.16 vs -2.37, *P*=.0058), and mean number of days when they used acute migraine medications (-3.88 vs -2.52, *P*=.041).[35]

Although not a pharmaceutical option, it would be remiss not to include behavioral therapies in this discussion. Cognitive behavioral therapy, mindfulness, relaxation, and biofeedback are effective in reducing migraine attack frequency and disability by helping individuals to develop coping mechanisms and avoid maladaptive thoughts. This is a valuable option for those seeking to avoid medications and

adverse side effects, as well as those who are pregnant or have comorbid conditions that present contraindications to certain pharmacologic options. Behavioral migraine management has been shown comparable to initiating treatment with a β-blocker.[36] More importantly, the combination of behavioral migraine management and a β-blockade improved outcomes of optimized acute treatment more so than monotherapy with either. This supported earlier findings that the combination of pharmacologic therapy plus biofeedback-assisted relaxation was superior to pharmacologic therapy alone in the long-term management of migraine with analgesic overuse.[37]

Neuromodulation is another viable nonpharmaceutical avenue utilized in migraine treatment. Neuromodulatory devices use electrical currents or magnets to stimulate the nervous system to alter pain signals. There are 3 devices approved and currently available for the preventive treatment of migraine: electrical trigeminal nerve stimulation (eTNS),[38] noninvasive vagus nerve stimulation (nVNS), and single-pulse transcranial magnetic stimulation (sTMS).[39] The combined occipital and supraorbital transcutaneous nerve stimulation device (eCOT-NS) is FDA approved for the acute treatment of migraine, but not yet available for use in the US.[40] These devices should be considered in those who are unable to tolerate or have contraindications to preventive agents and in those who prefer non-pharmacologic options. They may also be a preferable option in pregnant individuals, children, and elderly patients.[16]

Summary

Polypharmacy in the treatment of migraine is a controversial subject. Although monotherapy is the superior option, in a polygenic disease such as migraine, polytherapy with different mechanistic approaches is a viable option for those whose attacks are refractory to monotherapy. In select individuals, after a careful discussion of risks and benefits, it may serve as another tactic for clinicians to consider incorporating into treatment plans. ■

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