

A SPECIAL REPORT

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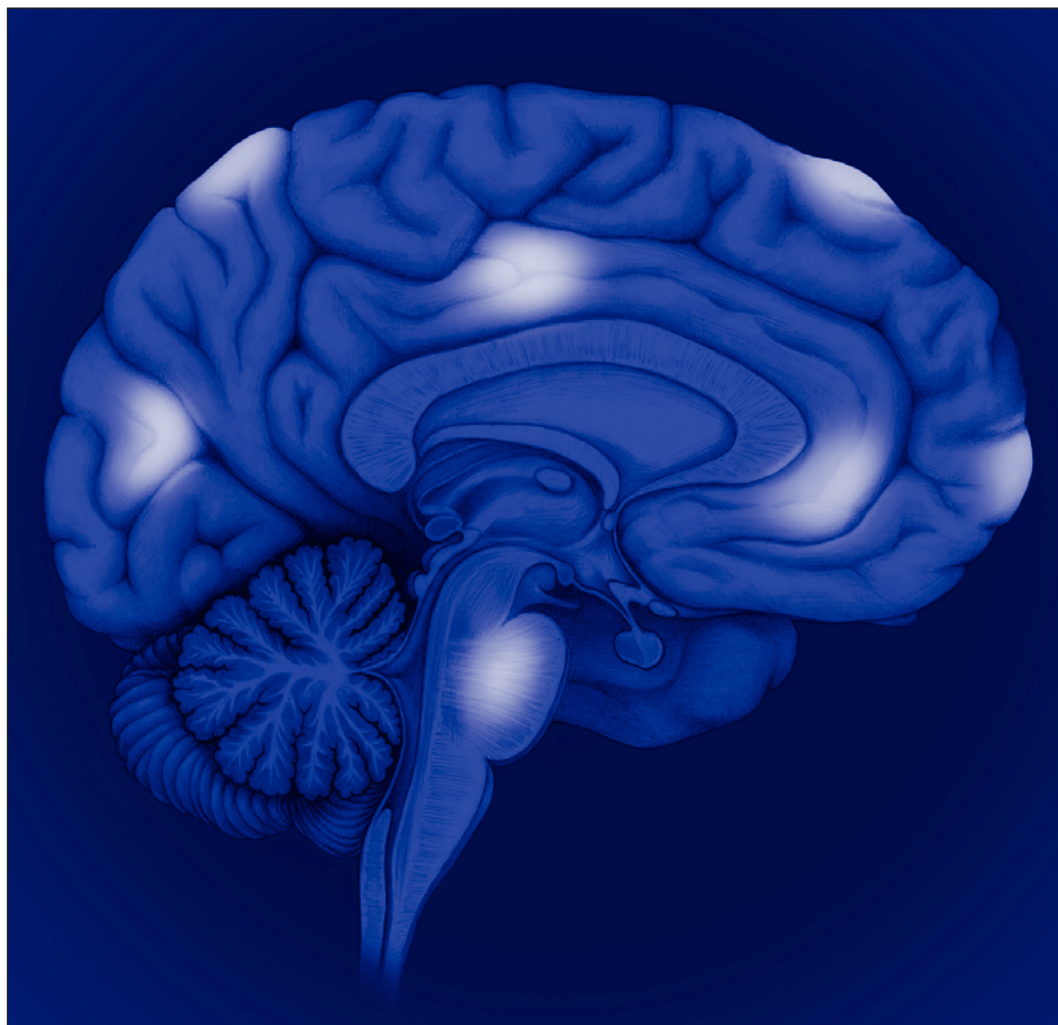
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Targeting Multiple Mechanisms: New Advances in Migraine Treatment

- An update on migraine pathophysiology and mechanism-based pharmacotherapeutics for migraine
- Migraine headaches: Treatment limitations and opportunities
- Combination therapy in acute migraine treatment: The rationale behind the current treatment options
- Use of combination therapy in migraine: A review of the clinical evidence



A SPECIAL REPORT

This *Postgraduate Medicine* Special Report, "Targeting Multiple Mechanisms: New Advances in Migraine Treatment," was sponsored and prepared for publication by Scienta Healthcare Education® and supported by an educational grant from GlaxoSmithKline.

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Statement of need

A main therapeutic goal in migraine is to achieve rapid freedom from pain, thereby allowing return to normal functioning. Over recent years, much work has been done to further this goal. Basic science research has yielded new information about the pathologic processes underlying migraine, most of which primarily affect the trigeminovascular system. Likewise, complementary clinical research initiatives have led to the development and evaluation of optimal migraine management strategies. Use of multi-mechanism combination therapy is one such strategy. It involves aborting migraine attacks via use of more than one pharmacotherapeutic agent so that limitations of monotherapy can be overcome; for example, multiple mechanisms can be targeted and synergy between agents can be established. As use of this strategy evolves, delivery of clinical content and skills training through ongoing medical education activities is warranted. This CME supplement provides useful information to help meet this need.

Educational objectives

At the conclusion of this activity, participants should be able to

- Identify specific mechanisms that underlie the pathogenesis of migraine.

- Describe the benefits and challenges associated with use of monotherapy to abort migraine attacks.
- Explain how using therapy to target multiple mechanisms in migraine can improve patient outcome.

Target audience

This activity is designed for primary care providers, neurologists, headache specialists, and other healthcare professionals who have an interest in the diagnosis and treatment of migraine.

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Introduction

Stephen Brunton, MD

■ Over the past decade, the armamentarium used to treat migraine has grown, and migraine care has been greatly optimized. Despite enormous progress, however, use of monotherapy to abort migraine attacks leaves room for improvement. Thus, multimechanism therapy—the use of 2 or more carefully matched therapeutic agents administered together and aimed at different underlying pathologic processes—has become the focus of increased attention in recent years and will be spotlighted in this supplement.

Featured in this supplement are 4 important articles that take the reader from a conceptual understanding of migraine pathophysiology to an exploration of relevant patient outcomes. An authoring team consisting of one neurology specialist and one generalist has written each article in order to present a balance of scientific, clinical, and practical perspectives. I offer sincere thanks to the distinguished faculty who have contributed.

The first article, by Cady and Biondi, reviews the cur-

rently existing hypotheses regarding migraine pathophysiology, with emphasis on specific mechanisms within the trigeminovascular system. Knowledge of these mechanisms provides a conceptual framework for understanding the antimigraine targets that serve as the basis for current and emerging pharmacotherapy options for migraine.

The second article, by Kaniecki and Hutchinson, outlines current empiric data about the drug classes and delivery systems most commonly used as abortive therapy for migraine and identifies existing and emerging drug formulations. For each class and delivery system, the advantages are highlighted and the limitations are articulated to uncover opportunities to improve their usefulness and address clinical challenges.

The latter 2 articles discuss the rational use of multimechanism polytherapy for migraine and share relevant clinical outcomes data. The article by Silberstein and Ruoff explains how the pharmacodynamic and

pharmacokinetic interplay between 2 carefully chosen agents can be capitalized upon to develop enhanced therapy regimens. This article persuasively argues for use of multimechanism therapy by pointing out its biologic plausibility and long tradition of successful use for treating other chronic medical conditions. In the concluding article, Taylor and Smith review clinical studies that used dual therapy or polytherapy for migraine.

Overall, the goal here is to ensure that prescribing clinicians appreciate the complementary modes of action of agents commonly used as abortive therapy for migraine attacks. That appreciation will help clinicians determine how agents can be combined in a multidrug regimen to achieve optimal therapeutic outcomes. I hope that this supplement will provide you with timely and insightful information that proves invaluable to your clinical practice as you construct optimal therapeutic regimens for migraine patients. ■

An update on migraine pathophysiology and mechanism-based pharmacotherapeutics for migraine

Roger K. Cady, MD, and David M. Biondi, DO

Preview

The pathophysiologic mechanisms of migraine are complex but appear to primarily involve the trigeminovascular system. Within this system, a number of factors may contribute to the generation and perpetuation of pathophysiologic changes leading to migraine. Current migraine medications exert their therapeutic benefit via actions at various points relating to these pathophysiologic changes. However, no single agent currently exists that targets all the hypothesized anatomical and cellular mechanisms of the migraine process. A future strategy for achieving optimal therapeutic effect and improving clinical outcomes in migraine involves rational targeting of the multiple mechanisms involved in its pathophysiology; conceptually, this may require concomitant use of multiple pharmacotherapeutic agents.

Introduction

Migraine is a common disorder afflicting approximately 9% of individuals in western countries and 11% of Americans in particular.¹ Among those individuals with migraine, disability is high, with over half reporting that migraine has a severe impact on daily life.¹ Although much of the disability from migraine can be

attributed to patients who fail to seek treatment, more than two thirds of treated patients report that therapy is not consistently effective.¹ The advent of triptans into the marketplace over a decade ago has done much to advance effectiveness of migraine therapy; however, triptans are not a panacea for all patients, and further therapeutic improve-

ments are needed. Often therapeutic failure is attributable not only to medication alone but also to limited understanding of the disease process and failure to employ appropriate treatment strategies.

One important key to the improvement of migraine treatment lies in fully understanding migraine pathophysiology. This knowledge will inspire targeted development of future therapies and optimal use of currently existing therapies. Unfortunately, the pathophysiology of migraine is complex and not yet fully understood; however, a number of neural substrates, circuits, and endogenous substances have been implicated in the various stages of the migraine process. With emerging developments and improved understanding of migraine mechanisms, we can begin to explain some of the previously inexplicable clinical features of a migraine attack and its variable response to pharmacologic treatments. This article reviews current hypotheses on the various processes involved in migraine pathophysiology and the pharmacologic actions of commonly used migraine medications.

Susceptibility to migraine

Studies in twins suggest that the origin of migraine has both a genetic and environmental component.² Studies in patients with familial hemiplegic migraine, a rare form of migraine, have provided insight into a possible genetic origin of migraine and indicate that mutations producing neuronal membrane channelopathies may play a role in the susceptibility to migraine.³ These channelopathies are

hypothesized to produce neuronal hyperexcitability; that is, they lower the threshold for neuronal firing in patients with migraine. Other abnormalities such as mitochondrial dysfunction and low concentrations of cellular or circulating magnesium may also play a role in neuronal hyperexcitability.⁴ Whether any or all of these abnormalities exist in most migraine patients, including those with the most common form of migraine—migraine without aura—is unknown.

Studies employing functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) support the notion of neuronal hyperexcitability in migraine. Stimulation of occipital cortex via a TMS device was shown to produce visual phenomena of flashing or sparkling lights (phosphenes) at a stimulation intensity that was lower in patients with migraine compared with control subjects. Furthermore, headaches were triggered by TMS in the majority of these migraineurs although no control subjects reported headache.⁵ fMRI studies of spontaneous or visually induced aura also imply an abnormality in neuronal excitability in the occipital cortex of migraine patients.^{6,7} Results from these studies suggest that the electrophysiologic correlate of migraine visual aura manifests as a slowly spreading wave of neuronal depolarization followed by a longer-lasting suppression of neuronal activity in the occipital cortex. This neurogenic phenomenon (termed *cortical spreading depression* or *CSD*) was first demonstrated by Aristides

Leao in the 1940s using direct stimulation of rabbit cerebral cortex⁸ and has been observed in a variety of experimental paradigms since that time. The initiator of CSD in clinical migraine is not known, but it may arise from disruptions in central inhibitory neuromodulation incited by migraine triggers.⁹ As this dysmodulation of inhibitory processes progresses, a critical excitatory threshold is reached, and CSD is initiated. The hypotheses regarding the potential significance of CSD to the initiation of the migraine process are discussed below.

Initiation of the migraine process

CORTICAL SPREADING

DEPRESSION—To investigate the mechanisms by which CSD may trigger migraine, Bolay et al studied CSD in a rat model.¹⁰ After a pinprick or electrical stimulation of the cortex, CSD was propagated across the cortical surface. Transient increases occurred in cortical blood flow but prolonged increases in blood flow were detected in the middle meningeal artery (MMA). After transecting trigeminal nerve innervation to the meninges, the experiment was repeated and the prolongation of increased blood flow in the MMA was abolished. On the basis of these and other laboratory findings, Bolay and colleagues proposed a mechanism for migraine initiation whereby CSD initiates release of neuroactive substances (K^+ , H^+ , neurotransmitters, nitric oxide, and arachidonic acid) into the extracellular and perivascular space to cause depolarization of trigeminal nerve endings around meningeal blood vessels.¹⁰

By this mechanism, it is hypothesized that intracerebral events (ie, CSD) are able to trigger activation of extracerebral neuronal structures (trigeminal nerve terminals) in the meninges. In patients with migraine aura, CSD is thought to occur in cortical areas capable of generating clinical symptoms such as migrating visual or sensory phenomena. In cases of migraine without aura, it has been proposed that CSD occurs in “silent” brain areas,¹¹ although this has yet to be proved.

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION—Autonomic nervous system dysfunction is believed to play a significant role in migraine pathophysiology¹²⁻¹⁴; however, the precise mechanism of its contribution has been under considerable debate. Two recent theories suggest that either sympathetic¹⁵ or, alternatively, parasympathetic dysfunction¹⁶ play a predominant role in the triggering of migraine, although these theories might not be mutually exclusive.

Peroutka recently reviewed the published data on autonomic function in migraineurs and found that many physiologic measures and clinical features in these patients (such as plasma norepinephrine [NE] levels, adrenergic receptor supersensitivity, and orthostatic symptoms) were indicative of sympathetic nervous system hypofunction.¹⁵ Based on this review, he proposed that sympathetic hypofunction might be involved in the initiation of migraine. According to this hypothesis, genetically vulnerable individuals, when subjected to stress, may experience a prolonged or excessive activation of

the sympathetic nervous system. As demonstrated in animal models, this excessive sympathetic stimulation may eventually result in depletion of NE, while levels of sympathetic cotransmitters (for example, dopamine, adenosine, and prostaglandins) are increased. At some point (after an initial vasoconstrictive phase), the net effect of this process is vasodilation of meningeal vessels because of reduction in the vasoconstrictive effects of NE in combination with vasodilatory effects of the cotransmitters. Furthermore, because the sympathetic nervous system normally has an inhibitory influence on the trigeminal system, trigeminal neurons might become disinhibited by diminished sympathetic function. Therefore, trigeminal activation during a migraine attack could be triggered or facilitated by changes in the sympathetic nervous system during times of stress.¹⁵

Burstein and Jakubowski have also suggested that the autonomic nervous system is involved in migraine generation, but with a focus on parasympathetic dysfunction.¹⁶ They cite clinical observations of parasympathetic hyperfunction in migraine patients during attacks such as the common occurrence of lacrimation, rhinorrhea, and nasal congestion as well as evidence that blockade of the sphenopalatine ganglion (a parasympathetic ganglion) can reduce migraine pain. Other anatomic and physiologic evidence—such as the dense innervation of meningeal blood vessels by parasympathetic fibers and the ability of meningeal nociceptor activation to increase activity in the superior salivatory

nucleus (SSN) (a parasympathetic nucleus) in the brainstem—also suggests a potential for parasympathetic involvement in migraine. These authors propose that the SSN is a common locus in neuronal pathways that are activated by various potential migraine triggers (for example, smells, food or sleep deprivation, or stress) via projections from the cortical, hypothalamic, and brainstem areas related to those triggers. It is hypothesized that impulses from the SSN are transmitted by parasympathetic efferent fibers to the sphenopalatine ganglion and, ultimately, the meninges and meningeal blood vessels, resulting in terminal release of acetylcholine, vasoactive intestinal peptide (VIP), and nitric oxide, thereby initiating a cascade that leads to trigeminovascular activation (described in detail below).¹⁶

Both Peroutka's (2004) and Burstein and Jakubowski's (2005) hypotheses are attractive because they have the potential to explain the pathogenesis of migraine in patients who have migraine without aura. It has been troubling to some researchers that the initiation of migraine in patients who don't experience aura had to be explained on the basis that CSD was occurring in clinically silent brain areas (with little evidence to support this theory).¹⁷ However, with either of the theories stated above, CSD is not a necessary component of migraine pathogenesis. Migraine can be triggered by stress or other events that lead to meningeal vasodilation, without CSD as a part of the process.

Other differences in the early symptoms of migraine with aura

and migraine without aura remain to be explained on the basis of pathophysiology. For instance, migraine with aura typically has an abrupt onset (for example, a visual aura may be immediately triggered by a bright flash of light with headache emerging shortly after the aura), while migraine without aura tends to develop more slowly and may be preceded by a lengthy premonitory or prodrome phase. During this prodrome, patients experience nonspecific symptoms such as mood or cognitive changes, increased sensory sensitivity, or food cravings.⁹ The physiologic mechanisms underlying these nonspecific symptoms are not understood, but it has been hypothesized that diffuse, nonfocal changes in various brain areas (cortical and hypothalamic) and in neurotransmitter systems may be responsible.⁹ Further study is needed to elucidate the specific pathophysiologic mechanisms of prodrome and the differences between migraine with and without aura.

Mechanisms of head pain and other migraine symptoms

NEURAL CIRCUITRY OF HEAD PAIN AND RELATED SYMPTOMS— The meninges, as intracranial structures with significant sensory innervation, are believed to be a principle source of head pain in migraine. A generally accepted pathway for generation of this pain begins with depolarization of perivascular trigeminal nerve endings in pia mater—initiated by some direct trigger or reflex, and potentially described in any of the scenarios above or another, as yet, undefined mechanism.

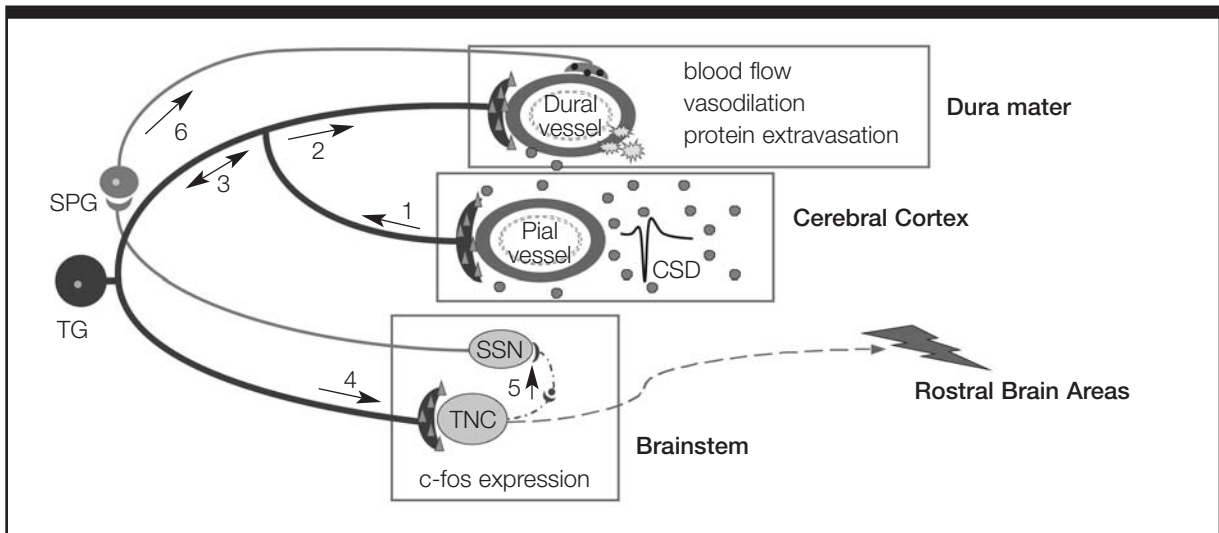


Figure 1. Proposed mechanism for the initiation of migraine headache pain by a wave of cortical spreading depression (CSD). CSD causes release of substances (eg, K^+ , H^+ , nitric oxide, adenosine, arachidonic acid [gray circles]) that activate perivascular trigeminal afferents sending impulses through the trigeminal ganglion (TG) to the trigeminal nucleus caudalis (TNC) (arrows 1, 3, and 4). Impulses from the TNC transmit rostrally to thalamus and cortical areas that process pain. Activation of TNC also leads to stimulation of the superior salivatory nucleus (SSN) (arrow 5) from which impulses are carried to the sphenopalatine nucleus (SPG) and back to the meninges (arrow 6), where vasoactive substances (VIP, nitric oxide, and acetylcholine [black circles]) are released. Direct or indirect (arrow 2) activation of dural trigeminal nerve endings results in release of substance P, CGRP, and neurokinin A (gray triangles), which may result in vasodilation and plasma protein extravasation.¹⁰

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Activation of pial nerve endings transmits impulses to the dura, stimulating release of vasoactive substances (for example, calcitonin gene-related peptide [CGRP], substance P, neurokinin A) in meninges. These impulses also transmit centrally through the trigeminal ganglion to the trigeminal nucleus caudalis (TNC) in the brainstem. The impulses then continue through the TNC via 2 pathways: one pathway transmits through the thalamus to cortical areas where head pain is perceived, and another pathway transmits impulses back up to the meninges via a parasympathetic arc through the SSN and sphenopalatine ganglion (Figure 1).¹⁰

Activation within the trigeminovascular circuit may also account for some of the

associated symptoms of migraine. Activation of the parasympathetic portion of the pathway may provoke the nasal symptoms that often accompany migraine.¹⁸ Similarly, the neck pain and stiffness that are commonly reported during migraine¹⁹ may be generated as a result of functional convergence of trigeminal neurons in the TNC and upper cervical spinal nerves.²⁰ Recruitment or functional convergence with other brainstem regions in close proximity to the TNC might underlie other migraine symptoms such as nausea, vomiting, photophobia, and phonophobia.²¹

Additionally, it is important to note that nontrigeminal brainstem nuclei (for example, periaqueductal gray, locus ceruleus) may play a role in

the generation or modulation of migraine head pain.³

NEUROGENIC INFLAMMATION AND PERIPHERAL SENSITIZATION—After the initial trigger for migraine (for example, a wave of CSD) and its consequential effect on the trigeminal system subsides, how does pain continue to be generated within the trigeminovascular system? One explanation suggests that *neurogenic inflammation* contributes to the continued generation of head pain.²² Since trigeminal and parasympathetic nerve activation stimulates the release of vasodilatory and inflammatory substances from nerve terminals (for example, substance P,²³ neurokinin A,²³ CGRP,^{23,24} VIP,²⁵ and prostaglandins²⁴), this theory posits that vasodilation and plasma protein extravasation (PPE) or

a neurogenic inflammatory process is produced in the meninges. After the initial activation of trigeminal nerve terminals by the migraine trigger, this process of neurogenic inflammation may take over, producing a vicious cycle of neuropeptide release and perivascular trigeminal nerve activation. Sensory impulses would be continuously generated and the ensuing cascade of cellular and molecular events would produce hypersensitivity of trigeminal sensory terminals to stimuli that are normally innocuous, such as pulsating arteries or head movement after the original activating trigger has ceased.²⁶ During migraine, these stimuli become the basis for many of the painful characteristics of migraine such as throbbing and pain with head movement. This cycle of activation is the *peripheral sensitization* phase of migraine.²⁷

This theory has been challenged recently, however. Some investigators have suggested that the scientific evidence supports only the vasodilatory component of neurogenic inflammation (primarily an effect of CGRP) but not PPE as a significant factor in peripheral sensitization.^{28,29} Most recently, the importance of CGRP-induced vasodilation has been questioned as well. Using electrophysiologic monitoring in a rat model, Levy and colleagues demonstrated that topical or systemic administration of CGRP provoked vasodilation in dural vessels but *did not* activate or sensitize meningeal nociceptors.³⁰

CUTANEOUS ALLODYNIA AND CENTRAL SENSITIZATION—Sensory signals generated in the skin by normally nonnoxious

stimuli such as hair combing, shaving, or touching the scalp are often reported as painful or unpleasant during migraine attacks.³¹ This clinical phenomenon is termed *cutaneous allodynia* and is believed to result from sensitization of central trigeminal pathways, specifically within the TNC. This sensitization occurs as a result of the constant barrage of impulses into the TNC from the already sensitized trigeminal nociceptors in the dura. Since the TNC also receives input from peripheral sensory nerves that serve the skin and muscles of the neck and upper torso, sensory signals from these areas can be misinterpreted and cause these extracranial regions to become hypersensitive to sensory stimuli.³¹ A recently proposed molecular mechanism for central sensitization stipulates that after peripheral nociceptors become sensitized, neurons and glia in the TNC become activated, causing release of prostaglandins. Neuronal release of prostaglandins is believed to facilitate prostaglandin release from the glia. The release of prostaglandins from glia completes a self-sustaining loop of excitation by promoting hyperexcitability in nearby neurons (neuronal recruitment).³² Via this mechanism, the TNC can be activated even in the absence of input from peripheral nociceptors. This mechanism is supported by evidence from a clinical study that showed effectiveness of IV ketorolac (a nonsteroidal anti-inflammatory drug [NSAID] that prevents formation of prostaglandins) in migraine patients with allodynia (in other words, after central

sensitization had developed).³² Additionally, in a rat model of migraine, electrophysiologic recordings showed that both ketorolac³² and naproxen³³ were able to desensitize sensitized TNC neurons. Clinical studies with oral NSAIDs are needed to further test this hypothesis.

Mechanism of action for common abortive migraine therapies

As noted above, several important molecules and brain pathways have been identified as potentially major contributors to migraine pathophysiology. In order to appreciate the distinct actions of commonly prescribed migraine therapies, their putative impact on these pathophysiologic mechanisms is reviewed below.

TRIPTANS AND ERGOTS—Triptans and ergots are considered migraine-specific medications because of their agonist actions at 5HT_{1B} and 5HT_{1D} receptors, receptors believed to be localized at strategic positions within the trigeminovascular system. There are at least 3 actions of 5HT_{1B/1D} agonists that may inhibit potentially important processes within this migraine-producing system.^{21,29}

- 1. Direct vasoconstriction of meningeal vessels.** Activation of 5HT_{1B} receptors on smooth muscle in meningeal blood vessels provides a vasoconstrictive action. This vasoconstriction counteracts the vasodilatory component of neurogenic inflammation, a process that may contribute to peripheral sensitization.
- 2. Inhibition of neuropeptide release in meninges.** Activation of presynaptic 5HT_{1D} receptors on perivascular

trigeminal nerve endings inhibits release of substance P and CGRP, thereby decreasing both the PPE and vasodilatory components of neurogenic inflammation.

3. Inhibition of central neurotransmission in the TNC.

Activation of presynaptic 5HT_{1D} receptors on central axonal projections of the trigeminal nerve to the TNC inhibits release of substance P, CGRP, and glutamate to interrupt pain impulses from the periphery. These actions may prevent or inhibit the development of central sensitization.

In clinical studies, early use of triptans, during mild pain or before development of allodynia, has proven more effective than using them at later stages. Pain-free response is greater at 2 hours posttreatment^{34,35} and pain freedom is achieved earlier,³⁶ presumably because central sensitization is avoided. Recent laboratory work by Levy and colleagues suggests that it is the central actions of 5HT_{1B/1D} agonists that are the most critical for their migraine efficacy. In electrophysiologic studies where inflammatory mediators were applied to rat dura mater, sumatriptan was unable to block their peripheral effects (increased firing rates in trigeminal ganglia) even when administered simultaneously with the mediators. However, spontaneous firing rates in central neurons (TNC) were decreased by sumatriptan when it was given early, before development of central sensitization.³⁷

Results from these studies have thus prompted recommendations for early intervention

with triptans. Despite the controversy that has developed around this treatment strategy regarding the possibility that the designs of the clinical studies that evaluated early intervention were biased towards a positive outcome,³⁸ our clinical experience continues to suggest that early treatment, while migraine pain intensity is still mild, improves outcome.

Other central (but non-trigeminal) sites of action have been suggested for 5HT_{1B/1D} agonists. The periaqueductal gray is a possible site since naratriptan injections into it decrease response of the TNC to dural stimulation.³⁹ Additionally, 5HT_{1B/1D} agonists may exert antiemetic actions via 5HT_{1D} receptors in the solitary tract nucleus, a structure known to modulate pain-induced nausea and vomiting.²¹ Whether triptans are able to exert action in these regions of the central nervous system in routine clinical use is unknown.

Although the mechanism responsible for the efficacy of triptans and ergots is similar (related to 5HT_{1B/1D} receptor agonism), their adverse event profiles differ because of the nonselective effects of ergots. Ergots' affinity for other 5HT receptors, in addition to adrenergic and dopaminergic receptors, is likely responsible for their side effect profile. Nausea, vomiting, weakness, and vascular effects are prominent side effects with ergots, although the tolerability profile of dihydroergotamine is somewhat improved.²¹ Both triptans and ergots are contraindicated in patients with ischemic cardiac, cerebrovascular, or peripheral

vascular disease, and concomitant use of these drugs is prohibited in all patients.

NSAIDs—NSAIDs are a class of analgesic drugs that reduce pain and inflammation at least in part by inhibiting formation of prostaglandins. This inhibition takes place because NSAIDs block cyclooxygenases (specifically COX-1 and/or COX-2) from converting arachidonic acid to prostaglandin G, the rate-limiting step in the prostaglandin cascade.⁴⁰ Therefore, the efficacy of NSAIDs in migraine⁴¹⁻⁴³ is likely a result of their antiprostaglandin effects within migraine pathophysiology. Although the precise role of prostaglandins within migraine is not established, it is known that infusion of prostaglandin E₁ precipitates headache in control subjects⁴⁴ and prostaglandins are elevated in the jugular blood of migraineurs during migraine.⁴⁵ On a molecular level, prostaglandins decrease firing thresholds of neurons, increase neuronal response to a suprathreshold stimulus, and augment release of substance P and CGRP, which allows their participation in neurogenic inflammation and hyperalgesia.⁴⁶ It is possible that prostaglandins may affect at least 3 crucial phases of the migraine process as noted in the above discussion of pathophysiology. The effects of NSAIDs on prostaglandins within these phases of migraine may include the following:

1. Reduction in probability that a migraine is triggered.

NSAIDs may reduce hyperexcitability of neurons and the probability of triggering migraine in at least 2 ways: (1) They may block the

formation of prostaglandins from arachidonic acid released by CSD.¹⁰ This action would decrease hypersensitivity in perivascular trigeminal nerves, potentially avoiding the initial neural activation required to generate migraine. (2) Similarly, if migraine patients have increased basal (interictal) prostaglandin levels because of sympathetic hypofunction,¹⁵ NSAIDs may decrease these levels, thereby reducing the chances that a migraine will be triggered. The proposed actions of NSAIDs on migraine initiation may explain their efficacy in the *prevention* of migraine.⁴⁷⁻⁴⁹

- 2. Inhibition of neurogenic inflammation.** Prostaglandin release may be stimulated by activation of trigeminal nerves and can contribute to neurogenic inflammation in the meninges.²⁴ NSAIDs, by blocking prostaglandin synthesis, would potentially reduce peripheral sensitization via reduction of vasodilation and PPE.
- 3. Abolishment of established central sensitization.** If sensitization of the TNC occurs because of prostaglandin release in neurons and glia, as proposed by Jakubowski and colleagues (see above), then the ability of NSAIDs to inhibit this release explains their apparent capacity to interrupt established sensitization.³²

OPIOIDS—Opioids are narcotic analgesics with widespread effects in the nervous system. Most opioid analgesics used for migraine bind preferentially to μ -opioid receptors

and are agonists at this receptor.⁵⁰ Butorphanol nasal spray, a mixed κ -opioid agonist/ μ -opioid partial agonist,⁵⁰ is the only opioid with proven efficacy in migraine.⁵¹

The mechanism of opioid analgesia is complex, but the primary actions in somatic pain relief can be described briefly. Opioids relieve physical pain by inhibiting ascending pain signal transmission at the level of the spinal cord dorsal horn while they also activate descending pain inhibitory pathways in the periaqueductal gray and medulla that project to the dorsal horn. Modulation of the emotional components of pain (that is, the distress caused by physical pain) by opioids is believed to occur in limbic structures.⁵²

A mechanism for opioid analgesia that is specific to migraine pain has been recently proposed and includes substrates that are also involved in triptan pain relief⁵⁰:

- 1. Inhibition of CGRP release in meninges.** Animal studies indicate that opioids block release of CGRP from trigeminal nerve endings and inhibit vasodilation caused by trigeminal nerve stimulation. This action may inhibit neurogenic inflammation and peripheral sensitization.
- 2. Inhibition of central neurotransmission in the TNC.** Similar to triptans, opioids are believed to act at presynaptic receptors on central trigeminal projections to prevent impulse transmission to TNC neurons. By doing so, opioids may prevent development of central sensitiza-

tion that occurs following meningeal vasodilation.

However, it is important to note that the abuse potential and sedative properties of opioids limit their use, and they are recommended in migraine only when other agents are contraindicated or ineffective.⁵¹

BARBITURATES—Barbiturates are CNS depressants with actions throughout the CNS. This depressant effect is primarily mediated via enhancement of GABAergic neurotransmission at GABA_A receptors and inhibition of glutamatergic transmission at AMPA receptors.⁵³ Within the trigeminovascular system, barbiturates may inhibit the transmission of pain signals in the TNC via GABA_A receptors.⁵⁴ Whether this action occurs primarily at a presynaptic or postsynaptic location is unknown; however, evidence suggests that postsynaptic receptors on the TNC are the most likely site of action.⁵⁵ Barbiturates are also likely to impact pain transmission at trigeminovascular sites via AMPA receptors.⁵⁶

Barbiturates are frequently prescribed for migraine treatment and are often used as first-line agents.⁵⁷ However, use of these agents, particularly butalbital combinations, is controversial because their efficacy has not been proven in placebo-controlled trials and because of their ability to cause medication overuse headache and drug dependence. The US Headache Consortium recommends limited use of these compounds and only with careful monitoring.⁵⁸

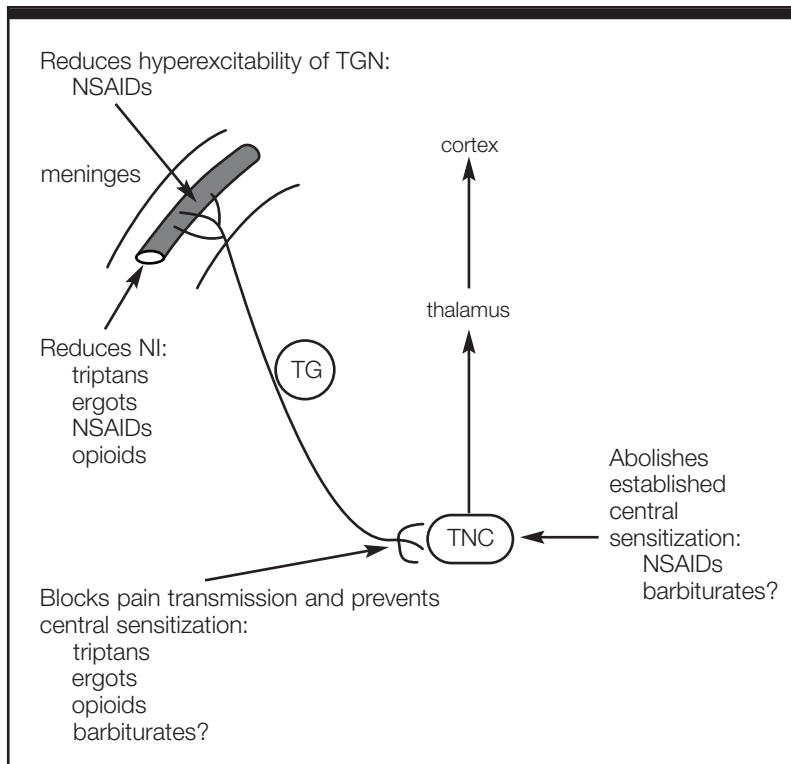


Figure 2. Proposed mechanisms of action for migraine medications within the trigeminovascular system.

NI, neurogenic inflammation; NSAIDs, nonsteroidal anti-inflammatory drugs; TG, trigeminal ganglion; TGN, trigeminal neurons; TNC, trigeminal nucleus caudalis.

Figure 2 provides an overview of the mechanisms of action within the trigeminovascular system for the commonly prescribed migraine medications.

Conclusions

The known pathophysiologic mechanisms underlying migraine are complex and multifactorial but allow for

intervention at multiple sites within the process to prevent or abort migraine attacks. New drugs to target sites not affected by current therapies are needed and recent clinical data show that some may be on the horizon. Preliminary efficacy has been demonstrated for antagonists of CGRP⁵⁹ and glutamate.⁶⁰

The targeting of multiple mechanisms simultaneously with more than one medication is another logical approach towards more quickly and effectively aborting migraine. Early use of triptans or ergots may reduce neurogenic inflammation and prevent central sensitization, while NSAIDs add the capacity to abort established central sensitization. Use of opioids should be limited because of their abuse potential and sedative effects, but when other medications fail, opioids may play a role similar to that of triptans and ergots in the disruption of processes underlying migraine pathophysiology. The role of barbiturates is less clear. ■

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Migraine headaches

Treatment limitations and opportunities

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Preview

In recent years, migraine treatment options have expanded to the extent that the practicing clinician now has a myriad of pharmacologic agents in varied drug classes and delivery systems from which to choose. Drug classes most commonly employed for treatment of migraine attacks include non-migraine-specific agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, barbiturates, combination analgesics, and antiemetics, and migraine-specific agents, such as triptans and ergot alkaloids and derivatives. Delivery options range from conventional, orally disintegrating, and rapid-release tablets to injection, nasal spray, and suppository. The US Headache Consortium offers guidelines classifying migraine treatments into different groups based on evidence of clinical benefit (Table 1).¹ Clinicians must be aware of the advantages and limitations of each class and delivery system and possible opportunities to improve their usefulness in different clinical contexts.

■ Treatment response and patient satisfaction in migraine are still not optimal.^{2,3} Patients typically prefer oral agents,^{2,4} but the gastric stasis that occurs during migraine⁵ slows down their absorption, and the nausea and vomiting experienced by many migraineurs can make oral agents difficult to take and/or retain.⁴ Alternative delivery systems pose other advantages and disadvantages.

Improving treatment outcomes requires arriving at the best combination of agent and strategy for each patient, and some troubleshooting may be required in terms of dosing, delivery system, and individual patient factors.^{4,6,7} Opportunities to increase treatment success, such as combining existing therapies and using a prokinetic agent to enhance the absorption of oral agents, are being explored.

Drug classes used in migraine: Advantages and limitations

NONSPECIFIC AGENTS—

Nonsteroidal Anti-inflammatory Drugs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are general analgesics that reduce inflammation by blocking cyclooxygenase (COX) enzymes, thereby inhibiting prostaglandin synthesis. NSAIDs are widely available and include over-the-counter agents, such as ibuprofen and naproxen, and prescription drugs, such as ketorolac and indomethacin. They are available as oral, injection, and suppository formulations. While oral NSAIDs are recommended as first-line therapy for mild-to-moderate migraine,¹ they are generally not as effective for severe migraine; and patient satisfaction with them for severe pain tends to be low.⁸ Although NSAIDs generally have fewer potential side effects than many other migraine treatments, they can cause gastrointestinal problems, such as nausea, vomiting, dyspepsia, and ulcer, and can lead to end-organ toxicity.^{7,9}

Opioids. Opioids, such as morphine, codeine, and butorphanol, block specific pain receptors in the brain and spinal cord to inhibit the transmission of pain signals. Possible side effects include sedation, nausea, and constipation, and frequent use can lead to headache progression (medication overuse headache) and dependence. Opioids are not recommended as a first-line treatment for migraine. However, they may be useful in limited circumstances as rescue therapy when NSAIDs and migraine-specific agents are contraindicated or have failed.^{1,6}

Table 1. US Headache Consortium Guidelines for Some Common Migraine Treatments¹

Drug	Adverse effects	Role (by consensus)	Evidence group*
Naratriptan	Infrequent	Moderate to severe migraine; less severe migraine when nonopiate medications fail	I
Rizatriptan	Occasional		
Sumatriptan	Occasional		
Sumatriptan nasal spray	Occasional	Moderate to severe migraine; useful when nonoral route needed; less severe migraine when nonopiate medications fail	I
Sumatriptan SC	Frequent	Moderate to severe migraine; useful when nonoral route needed; less severe migraine when nonopiate medications fail	I
DHE SC/IM	Occasional	Moderate to severe migraine; less severe migraine when nonopiate medications fail	II
DHE IV plus antiemetics	Frequent	Status migrainosus; therapy of choice in emergency department	I
DHE nasal spray	Occasional	Moderate to severe migraine; less severe migraine when nonopiate medications fail; low recurrence	I
Ergotamine	Frequent	Consider for selected patients with moderate to severe migraine	III
Metoclopramide IM	Infrequent to occasional	Adjunct therapy; may be choice for acute therapy	III
Prochlorperazine PR/IM	Occasional	IM/IV adjunct first-line therapy in emergency department or office; consider PR as adjunct	II
Acetaminophen	Infrequent	Pregnant migraineur	IV
Ketorolac IM	Infrequent	Consider in emergency department	II
Acetaminophen/aspirin/caffeine	Infrequent	First line for migraine	I
Butalbital/ASA/caffeine	Occasional	Occasional use for moderate to severe migraine; limit use because of risk of overuse	III
Butorphanol nasal spray	Frequent	Moderate to severe migraine; rescue therapy; limit use	I
Opiates—oral combinations	Occasional	Moderate to severe migraine; rescue therapy; limit use	II
Opiates—parenteral	Frequent	Reserved for emergency department use or rescue medication; limit use	II

* Group I: Proven, pronounced statistical and clinical benefit (at least 2 double-blind, placebo-controlled studies and clinical impression of effect); Group II: moderate statistical and clinical benefit (1 double-blind, placebo-controlled study and clinical impression of effect); Group III: proven statistically but not clinically effective or proven clinically but not statistically effective (conflicting or inconsistent evidence); Group IV: proven to be statistically or clinically ineffective (failed efficacy versus placebo).

Adapted from Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-62.

Opioids are available in oral, injection, nasal spray, and suppository formulations.

Barbiturates. These sedative agents (for example, butalbital), which depress the central nervous system by enhancing the action of gamma aminobutyric acid, are prescribed for occasional use in moderate to severe migraine.¹ Drowsiness is the most common side effect; less common side effects include dizziness, lightheadedness, and movement difficulty. Barbiturates must be used cautiously because of high rates of dependence and gradual headache escalation via the medication overuse (rebound) phenomenon.¹

Combination Analgesics. Oral combinations of analgesics and other nonspecific drugs, including a combination of isometheptene (a vasoconstrictor), dichloralphenazone (a sedative), and acetaminophen and combinations of aspirin or acetaminophen with caffeine and butalbital, are also available. Although these fixed combinations are commonly used, there is no evidence to support the use of butalbital compounds^{6,10} and little evidence to support the use of isometheptene compounds in acute migraine.^{1,6}

Antiemetics. Antiemetics are often used to treat nausea associated with migraine attacks and are sometimes used to treat the migraine directly. Specifically, metoclopramide is a dopamine D₂ receptor antagonist, 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist, and 5-hydroxytryptamine₄ (5-HT₄) receptor agonist¹¹ that is often used for nausea in migraine and can be administered as IV monotherapy for

pain relief.¹ Other antiemetics commonly used for migraine treatment include prochlorperazine and chlorpromazine.¹ Side effects of antiemetics include dizziness and sedation, and with the neuroleptic agents, there is a risk of extrapyramidal side effects such as dystonia. Routes of administration include oral, injection, and suppository.¹

MIGRAINE-SPECIFIC AGENTS—

Triptans. Triptans have generally become the standard of care for many patients with migraine.¹ These selective 5-HT_{1B/1D} receptor agonists are thought to work mainly by reversing vasodilation and inhibiting the transmission of pain signals peripherally and centrally by blocking the release of neuropeptides. They act directly on the migraine pain rather than simply alleviating general pain or providing sedation. Triptans have superior capability to treat migraine successfully compared with older treatments, offering greater speed of relief and consistency of effect as well as good tolerability.¹² Seven triptan agents have been approved in the United States since the early 1990s, all of which have comparable efficacy and tolerability.^{7,12} Triptans are available in conventional tablet, orally dissolving wafer, rapid release tablet, injection, nasal spray, and suppository formulations. They are also more effective when used early in the course of the migraine, while pain is mild.⁶ Early treatment is not appropriate in all attacks for patients with frequent or daily migraine, because of the risk of medication overuse.^{3,7}

Ergots. Drugs containing the ergot alkaloid ergotamine, a nonspecific 5-HT₁ receptor agonist that works through vasoconstriction of intracranial vessels and by inhibiting the release of vasoactive neurotransmitters,⁹ can be effective in moderate to severe migraine.¹ Possible side effects include toxicity, cardiovascular complications, nausea and vomiting, dizziness, tingling, muscle cramps, and abdominal pain. They are available in oral and suppository formulations.

Dihydroergotamine (DHE). DHE, a semisynthetic ergot alkaloid, is a treatment option in patients with moderate to severe migraine, and when it is administered intravenously along with an antiemetic, it is a first-line therapy for intractable migraine being treated on an inpatient basis.^{1,13} Colman and colleagues,¹³ in a systematic review of 11 studies, found 3 comparing DHE monotherapy to sumatriptan and phenothiazines. In these 3 studies, no benefit was found for DHE monotherapy over the other therapies. Regarding DHE, contraindications include ischemic cardiomyopathy, arterial hypertension, Raynaud's disease, and pregnancy.⁹ It is available as an injection and as a nasal spray.

Migraine drug delivery systems: Advantages and limitations

The different routes of administration of migraine treatments offer many options for delivering the drug to the part of the body that will help produce the best relief. Speed and efficacy are often maximized by nonoral formulations, particularly in those

patients with migraine upon awakening, rapidly building attacks, or significant gastrointestinal symptoms.^{4,6} A combination of more than 1 delivery system may be optimal for some patients, and studies have shown that patients prefer treatment options providing more than 1 formulation.^{4,14}

ORAL—The oral treatment route is the most common and is greatly preferred by most patients,¹⁵ and all migraine medications except DHE are available orally. However, the speed of onset and effectiveness of oral agents may be limited by gastric stasis that occurs during a migraine attack^{5,16} and interferes with optimal absorption of the drug. Because of inconsistent treatment outcomes, patients can become dissatisfied and discontinue therapy.⁴

Migraine has long been associated with gastric stasis, but until recently, no evidence was available to document its presence. Boyle and colleagues,¹⁶ using surface electrodes to measure gastric impedance, showed that there is a significant gastric delay during migraine attacks, but the measurements were indirect. In 2006, Aurora and colleagues⁵ used scintigraphy to determine gastric motility during and between migraine attacks in 10 migraine patients and 10 control patients matched by sex and age. Scintigraphy was performed once in all control subjects and migraine subjects in the interictal period and once in the ictal period in 9 of the migraine patients. The time to half emptying ($T_{1/2}$) both during and between attacks was longer in migraineurs compared with controls. Gastric stasis of

migraineurs between attacks was more severe than it was during attacks (a mean $T_{1/2}$ of 188.8 minutes versus 149.9 minutes, respectively) and was significantly greater than it was in control patients (111.8 minutes; $P < 0.05$). Gastric delay did not correlate with nausea. The investigators theorize that the gastric stasis that occurs during and between migraine attacks, as well as migraine-related nausea, may be caused by autonomic dysfunction.

Oral Triptan Formulations. Although triptans have greatly improved migraine treatment, outcomes with oral triptans still leave room for improvement. In a meta-analysis of 53 trials with oral triptans, Ferrari and colleagues¹² reported that a mean of 59% (95% CI, 57%-60%) of patients treated with sumatriptan 100 mg respond to treatment (from moderate or severe to mild or no pain) within 2 hours, 29% (95% CI, 27%-30%) achieve a pain-free response at 2 hours, 20% (95% CI, 18%-21%) have a sustained pain-free response over 24 hours, and 67% (95% CI, 63%-70%) have a consistent response at 2 hours in 2 out of 3 attacks. Similar results were seen with other triptans.

Of the oral-triptan formulations, the orally dissolving wafer, which can be taken without water and melts in the mouth, may provide convenience and discretion. The fact that it melts quickly can be an advantage for patients with nausea and vomiting or those who have difficulty swallowing tablets.⁴ However, because it is still swallowed (with saliva), it does

not provide faster relief than conventional tablets.⁴ Additionally, some patients consider the taste of an orally dissolving wafer to be unpleasant.¹⁷

The rapid-release tablet, by dissolving and dispersing more rapidly within the gastrointestinal tract, can provide faster relief and make it more likely that the drug will take effect during the crucial window of time early in the attack.¹⁸⁻²⁰ Sheftell and colleagues¹⁸ conducted 2 randomized, double-blind, parallel-group studies of 2,696 patients receiving rapid-release sumatriptan 50 mg or 100 mg or placebo. Results demonstrated that pain relief was achieved as early as 20 minutes for 100 mg and as early as 30 minutes for 50 mg with sumatriptan ($P \leq 0.05$).

Regardless of brand or formulation, evidence supports improved efficacy of oral triptans when administered during the earliest stages of acute migraine.^{3,6}

INJECTION—Injection is generally the fastest and most effective delivery system. Thus, it is a viable alternative for patients whose symptoms progress quickly, who awaken with symptoms that are already severe, or who cannot swallow a tablet because of severe nausea and vomiting.⁴ Issues with injections are that the actual injection can be painful, discomfort local to the injection site can occur, and many patients dislike needles. These issues may make it unlikely that this form of treatment will become widespread,⁴ yet patients do sometimes prefer it because of its speed and effectiveness.¹⁸

NASAL SPRAY—Nasal sprays provide a faster onset of action

than oral agents and another option for patients with nausea and vomiting^{4,21} without the invasiveness and inconvenience of an injection,²² and they can also be useful in patients with sinus symptoms.⁷ Nasal sprays can cause a bad or bitter taste in many patients,²¹ which could worsen nausea,⁴ and they can irritate the nasal mucosa.

Intranasal sumatriptan is rapidly absorbed, with 60% of the maximum plasma concentration occurring 30 minutes after a 20-mg dose.²² Peikert and colleagues, comparing intranasal sumatriptan with placebo in 544 patients in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, showed that intranasal sumatriptan (at doses of 5 mg, 10 mg, and 20 mg) is significantly better than placebo at providing 2-hour headache relief ($P \leq 0.01$) and is well tolerated.²¹ Most patients experienced a bad taste, which lasted up to 30 minutes in approximately 50% of patients, and 72% of patients who received the 20-mg dose said they would be willing to take it again.²² Zolmitriptan, another triptan, is also available as a nasal spray. The dose is 5 mg, and efficacy is comparable to that of sumatriptan nasal spray. Dodick and colleagues assessed the effectiveness of intranasal zolmitriptan in a multicenter, double-blind study of 2,122 patients randomized to receive zolmitriptan 5 mg nasal spray or placebo; the zolmitriptan group had a 2-hour response rate of 66.2% versus 35.0% for the placebo group ($P < 0.001$), and the drug was well tolerated.²³

Other nasal spray options include opioids and DHE.

Intranasal butorphanol has been associated with abuse and dependence, but it is still recommended as an option when other medications cannot be used or as a rescue medication if significant sedation would not pose a problem.¹

SUPPOSITORY—The rectal route is another option for patients with severe nausea and vomiting. Sumatriptan suppository is not presently available in the United States. Disadvantages of suppositories include erratic absorption, possible rectal irritation, fewer choices of agents, and a lower patient acceptance rate.⁴

Overcoming clinical challenges: Considerations for improving treatment outcomes

Migraine is a challenging disorder for both patients and clinicians. Improving treatment outcome will mean that clinicians will need to avoid diagnostic pitfalls, prescribe the optimal dose for the patient, and strongly consider use of multimechanism combination therapy.

AVOID DIAGNOSTIC PITFALLS—Migraine can initially be mistaken for tension or sinus headaches.⁶ Becoming familiar with a patient's pattern of headaches and symptoms can help the clinician and patient learn when early treatment might be warranted.⁷ Failing to diagnose a rebound headache is another potential misstep. If the patient is already using an over-the-counter drug, it can render other drugs ineffective and lead to medication overuse headache. Some patients may benefit from being evaluated for preventive treatment, particularly when attacks occur more frequently

than 1 to 2 days per week.

CHOOSE OPTIMAL DOSING—The optimal dose for treating migraine is generally the highest dose as listed on the package insert, except for very small or elderly patients.⁷ Titrating up, while common, may not be effective enough to stop the headache from progressing.

USE COMBINATION THERAPY TO TARGET MULTIPLE MECHANISMS—Combining existing therapies represents a possible opportunity to improve treatment response, as discussed in the article on combination therapy in this supplement. This strategy can target the multiple mechanisms and neurologic pathways that contribute to a migraine attack. The first article in this supplement discusses these pathways. Combination therapy is becoming the standard of care in many clinical conditions, and many combinations are already being used in migraine treatment.^{24,25} The last 2 articles in this supplement will provide rational argument for and clinical data supporting use of multimechanism combination therapy.

Conclusions

Clinicians must be aware of the clinical advantages associated with the therapeutic classes of agents and routes of administration most commonly used to treat migraineurs. Additionally, they must appreciate the limitations associated with currently available agents and formulations and stay abreast of new strategies being investigated to overcome these limitations. Such awareness will enable clinicians to design individualized treatment plans and provide appropriate patient counseling. ■

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NOTES

Combination therapy in acute migraine treatment

The rationale behind the current treatment options

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Preview

Combination therapy is used to treat many disorders; for some conditions, it has become first-line treatment or the standard of care. The development and use of novel drug combinations will grow as the understanding of disease pathophysiology and drug pharmacokinetics and pharmacodynamics progresses.

In the acute management of migraine, existing drug combinations have proven to be effective, safe, and tolerable. They may offer distinct advantages compared with monotherapy, including both enhanced therapeutic benefits and fewer adverse events (AEs). This article discusses the types of interactions that can occur with combination therapy and their potential effects on efficacy and tolerability. The rationale for using combination therapy will first be discussed within the context of clinical conditions in which it is already the standard of care. This will be followed by a discussion of the rationale for use in migraine.

Characterizing drug-drug interactions and their role in combination therapy

When 2 drugs are combined in the treatment of a disorder (or multiple disorders), a drug-drug interaction may occur. That interaction is characterized, based on its mechanism, as either a pharmacokinetic or a pharmacodynamic interaction.¹

- In a pharmacokinetic interaction, drug absorption, distribution, metabolism or excretion is altered for at least one of the drugs being combined, compared with when the drugs are used alone.
- In a pharmacodynamic interaction, drug pharmacokinetics remain unchanged, but the combined pharmacologic

effect is altered, compared with the effect of either drug alone.

A pharmacodynamic interaction may occur when combining 2 drugs with differing mechanisms of action that produce the same effect.¹ For example, the combination of aspirin (an inhibitor of platelet function) and warfarin (an inhibitor of Vitamin K–dependent clotting factors) will result in an increased anticoagulant effect.² Drugs that compete for the same receptor (but with opposing effects at that receptor) may also interact pharmacodynamically. This type of reaction has been exploited in the treatment of opioid-induced respiratory depression with naloxone (a μ -opioid receptor antagonist).¹

The effect of combining 2 drugs can be classified as additive, synergistic, or antagonistic.¹

- An **additive** effect occurs when the efficacy or side effects are equal to the sum of the effects of either drug alone
- A **synergistic** effect occurs when the efficacy or side effects are greater than the sum of the effects of either drug alone
- An **antagonistic** effect occurs when the efficacy or side effects are decreased compared with using either drug alone

A drug-drug interaction, whether it is a pharmacokinetic or pharmacodynamic one, is typically considered undesirable. In many situations (but not all), pharmacokinetic interactions should be avoided. Using a drug with a narrow therapeutic index in combination with a drug that will alter its rate of metabolism or excretion may result in toxic effects if the rate is decreased

or in inefficacy if the rate is increased. Pharmacokinetic interactions often occur with agents that are hepatically metabolized via the cytochrome P450 system. A medication that is an inhibitor or inducer of the particular enzymes that participate in the biotransformation of another agent may increase or decrease (respectively) the serum levels of that agent and negatively impact its safety or efficacy profile. Similarly, concomitant use of two drugs that are metabolized through the same CYP3A4 or CYP2D6 enzyme pathway increases the potential for a pharmacokinetic interaction.³

Pharmacodynamic interactions may also produce unwanted effects—some of them potentially life-threatening. As noted above, combining warfarin with aspirin will increase anticoagulant effects and in some cases, these increased effects may result in bleeding.² Combining 2 drugs that both produce CNS depression may also result in a serious interaction. For instance, combining an opioid analgesic and a benzodiazepine hypnotic may produce extreme somnolence, respiratory depression, or worse (coma and death). Dosage adjustments of either or both drugs may be required when there is a need to combine drugs that produce excessive effects when used together.⁴

On the other hand, drug combinations can be, and are being, rationally designed to produce beneficial drug-drug interactions. The ideal drug combination would have synergistic efficacy effects but antagonistic effects on toxicity. Most drug combinations have been devised with the intent of pro-

ducing better efficacy.⁵ Most commonly, an additive effect on efficacy is achieved via a pharmacodynamic interaction. Use of combination therapy has been standard treatment for a variety of disorders that are inadequately controlled by monotherapy.

The legacy of combination therapy

Use of multiple drugs to treat a single disorder is not a new concept. Combination therapy has been used in some clinical conditions for many years. It has the potential to improve outcome compared with monotherapy by targeting different parts of the pathophysiologic process. An additive or synergistic effect may be achieved, ideally with no worsening or even with improvements in tolerability. Drug bioavailability or rate of absorption may also be improved when pharmacokinetic interactions are exploited. Use of combination treatments is common or in some cases, standard of care, for a number of disorders treated in primary care including diabetes, hypertension, and various infectious diseases, particularly HIV.

TREATMENT OF TYPE 2 DIABETES: EMPLOYING A PHARMACODYNAMIC INTERACTION TO PRODUCE ADDITIVE EFFICACY EFFECTS—

In patients with Type 2 (non-insulin-dependent) diabetes, blood glucose levels are elevated because of 2 physiologic defects: resistance to the actions of insulin and impaired β -cell function in the pancreas resulting in decreased insulin production. Monotherapy for this disorder is associated with a high treatment failure rate, especially as the disease progresses.⁶

A multimechanistic approach to the treatment of Type 2 diabetes with oral therapy employs beneficial pharmacodynamic interactions between antidiabetic agents to target multiple aspects of diabetes pathophysiology.

- Sulfonylureas and non-sulphonylurea secretagogues (repaglinide, nateglinide) bind to the ATP-dependent potassium channel complex in the membranes of β -cells where they are able to potentiate glucose-dependent insulin secretion.⁷
- Biguanides (metformin) act through an uncertain mechanism that results in the potentiation of the suppressive effects of insulin on hepatic glucose production.⁷
- Alpha-glucosidase inhibitors slow the absorption of glucose by impairing the action of enzymes that break down complex carbohydrates in the small intestine.⁷
- Thiazolidinediones bind to peroxisome-proliferator-activated receptor- γ which alters gene expression and leads to an increase in insulin sensitivity in fat, liver, and muscle.⁷

Various combinations of these agents produce additive efficacy. For example, non-sulphonylurea secretagogues, which potentiate glucose-dependent insulin secretion (controlling postprandial hyperglycemia), are combined with metformin, which suppresses hepatic glucose production (controlling fasting hyperglycemia), to produce an additive effect on glycemic control.⁶

TREATMENT OF HYPERTENSION: EMPLOYING PHARMACODYNAMIC INTERACTIONS TO PRODUCE ADDITIVE OR SYNERGISTIC EFFICACY EFFECTS— Treatment of hypertension also benefits from a multimechanistic approach since its pathophysiology is complex and multifactorial.⁸ A common physiologic abnormality in hypertensive patients involves the renin-angiotensin system. In some patients, increased levels of renin and angiotensin II are a part of the pathophysiology driving hypertension. β -blockers are useful in this population because of their ability to suppress renin release, in addition to decreasing cardiac output.⁸ However, β -blockers also cause retention of sodium and water. To counteract this problem, clinicians combine a β -blocker with a thiazide diuretic, taking advantage of the diuretic's ability to increase sodium excretion and decrease blood volume. These diuretics also stimulate renin release, but this effect is counteracted by the β -blocker.⁹ Studies indicate that this combination may be additive or even synergistic, in the case of combining bisoprolol with hydrochlorothiazide. Low doses of each have been combined to produce substantial antihypertensive effects, but with a low incidence of side effects,⁹ suggesting a possible antagonistic effect on toxicity.

TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME (HIV/AIDS): EMPLOYING PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTIONS TO INCREASE EFFICACY— Disease processes may involve multiple, and often cyclical,

phases. Individual agents may be most effective against a specific phase of the disease cycle; if combined, these agents may interrupt the disease process across multiple phases. One example of a pharmacodynamic interaction that drives effective combination therapy by attacking multiple phases of the disease process is the use of antiretroviral combinations to treat HIV/AIDS.

Combination therapy is the standard of care even for the initial treatment of HIV/AIDS. Quadruple-agent and triple-agent therapy is used to target multiple mechanisms and phases of the replication cycle of HIV. Currently recommended antiretroviral agents fall into 3 main categories, based on mechanism of action¹⁰:

- Nucleoside reverse transcriptase inhibitors (NRTIs or nucleoside analogs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)

NRTIs and NNRTIs target the same early phase of the HIV replication cycle, but via slightly different mechanisms. NRTIs interfere in the viral replication cycle during the conversion of RNA to DNA. They inhibit reverse transcriptase from completing its function by competing with the natural nucleosides, which allows incorporation of the NRTI itself into DNA and terminates chain formation. Without the ability to replicate its own DNA, HIV cannot infect the cell. NNRTIs also interfere with reverse transcriptase but by binding directly to it and preventing it from converting RNA to DNA. PIs have their effect near the end of the

replication cycle: they prevent replication of mature, infectious HIV by blocking the enzyme (protease) that cleaves long chains of polyproteins (immature, noninfectious precursors) into smaller, functional chains that are able to infect other cells.¹¹ Current recommendations suggest initial therapy with at least 3 drugs, either 1 NNRTI + 2 NRTIs or 1-2 PIs + 2 NRTIs.¹²

Pharmacokinetic interactions are also exploited in HIV/AIDS treatment by using ritonavir, a PI with inhibitory effects on the CYP3A4 enzyme, to “boost” the effects of other PIs that are metabolized via the same enzyme. Metabolism of these drugs is slowed, causing increased exposure.¹² Use of combination therapy for HIV has been highly successful in suppressing viral replication, improving immune function, and reducing morbidity and mortality in patients with HIV.¹³

Combination therapy in the acute treatment of migraine headache

Combination therapy has a long tradition as migraine management.^{14,15} Combination therapy for acute migraine headache takes advantage of both pharmacokinetic and pharmacodynamic drug-drug interactions to achieve better efficacy or tolerability. Some combinations use a multimechanistic approach that targets different aspects of the pathophysiologic mechanism, taking advantage of pharmacodynamic interactions to improve outcome. With other drug combinations for migraine, pharmacokinetic interactions are exploited to speed up drug

absorption or slow down drug elimination. In some cases, migraine drug combinations have been designed in order to produce both pharmacodynamic and pharmacokinetic interactions that are beneficial to treatment. These interactions may produce either additive or synergistic effects on efficacy.

Combination therapy for migraine offers a variety of potential advantages when compared to traditional monotherapy for headache. A few examples of drug combinations for migraine and the rationale for their use are discussed below.

COMBINATIONS OF

TRIPTANS AND NAPROXEN: A PHARMACODYNAMIC AND POTENTIAL PHARMACOKINETIC INTERACTION—Triptans interact pharmacodynamically with NSAIDs since these medications are believed to impact different parts of the trigeminovascular system, the system thought responsible for the generation of migraine head pain through its connections with the meninges (for review, see the article titled *“An update on migraine pathophysiology and mechanism-based pharmacotherapeutics for migraine”* by Cady and Biondi in this supplement). Triptans are believed to interrupt the migraine process in 3 ways: by direct vasoconstriction of meningeal vessels, by inhibiting release of vasoactive substances (eg, CGRP) in the meninges, (reducing neurogenic inflammation), and by inhibiting central transmission of nerve impulses to the trigeminal nucleus caudalis (TNC). This is achieved via activation of 5HT_{1B/1D} receptors.¹⁶ Triptans decrease pain and prevent the develop-

ment of central sensitization (self-sustaining activation of the TNC) if taken early in a migraine attack.¹⁷ NSAIDs may also inhibit neurogenic inflammation by blocking formation of prostaglandins in the meninges, but additionally, they may have the capacity to interrupt established central sensitization since they may interfere with the glial production of prostaglandins.¹⁸ A pharmacokinetic interaction between triptans and NSAIDs may also play a role since coadministration of sumatriptan and naproxen appears to slow the elimination of naproxen from plasma.¹⁹

Two recent studies have evaluated the combination of a triptan and an NSAID for acute treatment of migraine. An open-label study compared rizatriptan monotherapy to 2 rizatriptan combinations: one that included rofecoxib (a COX-2-specific NSAID) and another that included tolfenamic acid (a traditional NSAID). Pain-free rates at 2 hours were significantly better for the combination that included rofecoxib compared with rizatriptan alone. The tolfenamic acid combination was not significantly better than monotherapy.²⁰ Since rofecoxib was not studied as monotherapy, the nature of this interaction (synergistic versus additive) cannot be determined. Adverse event rates were similar for the rofecoxib combination and rizatriptan monotherapy groups. The second study was double-blind and placebo-controlled.²¹ Sumatriptan (50 mg) plus naproxen (500 mg) was compared with sumatriptan alone, naproxen alone, and placebo. The combination was significantly more effective than

all other treatments for the primary endpoint, 24-hour (sustained) pain relief response. Our analysis of the differences in sustained relief rates (relative to placebo, ie, therapeutic gain) suggests a synergistic interaction between sumatriptan and naproxen (see Table 1). The overall adverse event rate was similar in the combination (23%) and sumatriptan monotherapy (24%) groups.

The caveats of using a triptan-NSAID combination thus far appear to be the same as using either agent alone since adverse events rates were not increased by use of the combinations. Traditional NSAIDs have been associated with gastrointestinal side effects²² and triptans are contraindicated in patients with ischemic cardiac, cerebrovascular, or peripheral vascular disease.²³ Rofecoxib has been withdrawn from the market because of its increased cardiovascular risk.²³

Caffeine-containing combinations: A pharmacokinetic and potential pharmacodynamic interaction

In the acute treatment of pain, caffeine has been shown to enhance the effect of a variety of analgesics.²⁴ The mechanism responsible for this enhancement is not fully known, but may involve both a pharmacokinetic and a pharmacodynamic interaction. Pharmacokinetic studies have shown that caffeine increases the rate or extent of absorption of aspirin,²⁵ ergotamine, and acetaminophen,^{24,26} which could explain the faster onset and increased pain relief obtained with the combinations. The pharmacodynamic contribution

Table 1. Analysis of Effects of Combined Therapy Versus Individual Components

Study	Efficacy Result* by Treatment Group				Therapeutic Gain (active response minus placebo response)			Type of Effect†
	SUM/NPX	SUM	NPX	PLA	SUM/NPX	SUM	NPX	
Smith et al	46%	29%	25%	17%	29	12	8	Synergistic 29 > 20
Diener et al	65 min	73 min	107 min	133 min	-68	-60	-26	Additive 68 < 86

* Primary efficacy variable was percent of patients with 24-hour (sustained) pain relief for the Smith et al study; for the Diener et al study, it was median time to 50% pain relief (in minutes).

† If the therapeutic gain in the combination group (ASA/AC/C or SUM/NPX) was greater than the sum of the therapeutic gains of the components comprising the combination, the combination was considered synergistic. If the gain in the combination group was less than or equal to the sum of the gains in the components, the combination was considered to have additive effects.

AC, acetaminophen; ASA, aspirin; C, caffeine; NPX, naproxen; PLA, placebo; SUM, sumatriptan.

of caffeine to increased efficacy is less clear because caffeine as monotherapy has not been proven effective in migraine, although it has shown some efficacy in other headache types.²⁷ The mechanism underlying any potential pharmacodynamic (multimechanistic) effect of caffeine may be related to its ability to block adenosine receptors.²⁸

Three studies have compared the efficacy of an analgesic with and without caffeine. In a study of patients with migraine without aura, diclofenac (an NSAID) plus caffeine was significantly better than placebo, whereas diclofenac alone was not. Whether this improved efficacy represented synergism or just an additive effect could not be determined since caffeine as monotherapy was not studied.²⁴ Another placebo-controlled study compared a triple combination of acetaminophen, aspirin, and caffeine to each agent alone and also to the combination of aspirin and acetaminophen in patients with migraine or tension-type

headache. The triple combination was significantly more effective than all the other treatments for the primary endpoint “time to 50% pain relief.” Adverse event rates were similar across groups.²⁹ Our analysis of the median time to 50% pain relief for the triple combination group compared with the double combination and caffeine monotherapy suggests that the addition of caffeine to acetaminophen and aspirin produced an additive, rather than a synergistic effect on efficacy (see Table 1). In the third study, a combination of tolfenamic acid and caffeine was compared with either agent alone and with placebo. Again, the combination therapy produced better efficacy than either agent alone (for migraine severity at 1.5 hours), although the differences were not statistically significant. Numerical data were not provided, but visual inspection of the graphic data suggested that the combination was only marginally better than tolfenamic acid alone and there was no synergistic effect.³⁰

Antiemetic-containing combinations: A pharmacokinetic and pharmacodynamic interaction

The nausea and vomiting associated with migraine is common and may be as disabling as the headache itself. Antiemetic agents such as metoclopramide have been used to treat these associated symptoms.³¹

Metoclopramide is a prokinetic agent that stimulates gastric motility and accelerates gastric emptying. Its prokinetic effects are thought to be mediated primarily by actions at the serotonin 5-HT₄ receptors in the upper gastrointestinal tract. Metoclopramide also has an antiemetic effect that stems from blockade of dopamine D₂ receptors in the CNS.³² Both effects may contribute to the added efficacy that has been seen with metoclopramide combinations. A pharmacokinetic interaction would be produced by the increased gastric motility since the coadministered agent would be absorbed more rapidly, while the antiemetic effects of metoclopramide would reduce

nausea and vomiting. The antiemetic effects contributed by metoclopramide could be considered a pharmacodynamic interaction, although that interaction does not occur within the pain-producing sites associated with migraine (ie, the trigemino-vascular system). Injectable dopamine antagonists have shown effects on migraine pain as well³¹; however, it is unlikely that oral agents could contribute to headache pain relief.³³

Two double-blind studies have evaluated the effects of oral metoclopramide in combination therapy for migraine. In a pilot study, Schulman and Dermott compared sumatriptan alone (50 mg) to a combination with metoclopramide in migraine patients who were previously unresponsive to triptans. They found a higher rate of headache relief at 2 hours with the metoclopramide combination (44%) than with sumatriptan alone (31%).³⁴ The difference was not tested for statistical significance. Without a placebo group or a metoclopramide monotherapy group, it is not possible to deter-

mine if the addition of metoclopramide produced a synergistic or additive effect. In the second study, Tokola and colleagues studied metoclopramide in combination with tolfenamic acid. The combination was statistically superior to metoclopramide alone (for migraine severity at 1.5 hours), but the difference compared with tolfenamic acid monotherapy did not reach statistical significance. Whether any synergism occurred with the combined product could not be determined because numerical data were not presented.³⁰

Because of its prokinetic effects, metoclopramide has the potential to be especially helpful in migraine because it may reverse the gastric stasis that has been documented in patients during migraine attacks.³⁵ However the side effects of metoclopramide such as sedation, orthostatic hypotension, and extrapyramidal symptoms may limit its usefulness.³⁶

Conclusions

Combination therapy is used to treat many disorders and is often

the most commonly used and effective treatments or, in some cases, the standard of care. The effectiveness of this strategy is derived from pharmacokinetic or pharmacodynamic interactions that produce either additive or synergistic effects. Many drug combinations, including those used in migraine, target multiple mechanisms within the disease process. The result is often increased efficacy with similar or better tolerability compared with monotherapy.

Combination therapy for acute migraine treatment is not uncommon: many combinations are recommended for treating headache in addition to the above examples.³¹ However, although the efficacy and safety of some combination treatments for migraine have been demonstrated, combination therapy is not yet considered the standard of care. Further study is needed to provide more information on combination therapy and may promote this strategy to "first-line" in patients with moderate to severe migraine. ■

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NOTES

Use of combination therapy in migraine

A review of the clinical evidence

Frederick Taylor, MD, and Timothy Smith, MD

Preview

The previous article in this supplement sets forth a compelling argument for use of multimechanism combination pharmacotherapy as a strategy to improve outcomes for patients with migraine. This article picks up where the previous one left off by providing a concise review of data regarding use of combined agents to treat migraine. Included in this review are clinical studies of both over-the-counter (OTC) and prescription agents whose performance in combination has been assessed in comparison to placebo and/or monotherapy. Also, this review is not limited to fixed drug combinations; studies that used different single-agent tablets administered together are also included.

OTC agents used in combination

Several studies using nonprescription agents have shown a benefit of combination therapy over monotherapy. A multicenter, randomized, double-blind, single-dose, placebo-controlled, parallel-group study compared the efficacy, safety, and tolerability of (1) 500 mg aspirin plus 400 mg acetaminophen and 100 mg caffeine, (2) 500 mg aspirin plus 400 mg acetaminophen, (3) 1000 mg aspirin, (4) 1000 mg acetaminophen, (5) 100 mg caffeine, and (6) placebo in an intent-to-treat set of 1,743 patients who were accustomed to

treating their episodic tension-type headache or migraine attacks with nonprescription analgesics.¹ For the primary endpoint “time to 50% pain relief,” the fixed combination of aspirin, acetaminophen, and caffeine was significantly superior to the combination without caffeine ($P = 0.02$) and to the single substances, aspirin ($P = 0.04$), acetaminophen ($P = 0.002$), caffeine ($P < 0.0001$), and placebo ($P < 0.0001$). The incidence of adverse events was low and tolerable.

Another study compared the combination of acetaminophen 500 mg, aspirin 500 mg, and

caffeine 130 mg with the single agent sumatriptan 50 mg in 171 migraineurs.² Patients kept diaries, which investigators used to ascertain whether the agents were effective in the early treatment of migraine. The results showed that the combination regimen was significantly more effective than sumatriptan in the early treatment of migraine, as shown by superiority in pain intensity reduction beginning at 2 hours after dosing and continuing throughout the 4-hour treatment period ($P \leq 0.011$), use of rescue medication ($P = 0.043$), and degree of disability by 4 hours postdose ($P = 0.044$). Additional comparator trials would be helpful in clinical practice decision making.

Triptans combined with other agents

The thrust of current research has been to combine the triptans with other medications. The therapeutic rationale is to counter more than one of the neurobiologic mechanisms related to migraine pathophysiology.

SUMATRIPTAN AND NAPROXEN—Sumatriptan and the other triptans are very effective in both the acute treatment of a migraine attack and as initial treatment choice in patients with moderate to severe migraine pain.³ They block pain transmission in the trigeminal system, cause vasoconstriction, and when given early in the attack, may prevent development of central sensitization.^{4,5} However, while they prevent the release of inflammatory substances from nerve endings, they do not appear to affect inflammatory substances already released or inflammatory processes already activated.⁵

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective migraine therapies,³ and in addition to their ability to prevent prostaglandin production, they can prevent the extravasation of plasma by acting on neuropeptide-induced changes in vascular permeability and/or smooth muscle contractility, as has been shown in preclinical studies.⁶ Thus, because of their different mechanisms of action on headache, a rationale exists for combining a triptan and an NSAID as an improved treatment over monotherapy. Srinivasu and colleagues demonstrated that naproxen did not alter the pharmacokinetics of sumatriptan when these agents were used concomitantly in healthy volunteers.⁷ However, in 2005, Wargin and colleagues demonstrated that naproxen pharmacokinetics were altered in healthy volunteers when naproxen was administered with sumatriptan. Specifically, absorption of naproxen was delayed.⁸

Several studies have been performed to assess the efficacy of sumatriptan and naproxen in migraine. A prospective study of 67 patients involved the administration of sumatriptan 100 mg and naproxen sodium 550 mg and assessed the recurrence rate of migraine.⁹ The patients had previously used sumatriptan 100 mg alone with success to treat prestudy migraines with a recurrence rate of 62.5%. This rate dropped to 14.2% ($P < 0.0001$) when the combination was used. In a double-blind substudy of that trial, 26 patients were randomized to be given sumatriptan plus placebo or sumatriptan plus naproxen at the aforementioned doses. The

recurrence rate of the triptan monotherapy was 59%, compared with 26% for the combination ($P < 0.0003$).

Another randomized study, which was double-blind, double dummy, and placebo controlled, involved 972 participants who each treated a single migraine episode with encapsulated sumatriptan 50 mg plus naproxen sodium 500 mg, each of the components used as monotherapy, or placebo.⁵ In the combination group, 46% of patients reached 24-hour pain relief response, which was significantly more effective than sumatriptan alone (29%), naproxen sodium alone (25%), or placebo (17%) ($P < 0.001$). Two-hour headache response was also significantly better in the combination group (65%) than in the sumatriptan group (49%), the naproxen sodium group (46%), or the placebo group (27%) ($P < 0.001$). The incidence of headache recurrence up to 24 hours after treatment was lowest in the combination group (29%), compared with sumatriptan alone (41%; $P < 0.05$), naproxen sodium alone (47%; $P = 0.004$), or placebo (38%; $P = 0.08$).

A recently developed sumatriptan tablet formulation has been shown to be bioequivalent to the conventional tablet; however, because of technology that causes rapid release and dispersion of drug, it has more rapid absorption than the conventional-tablet sumatriptan.¹⁰ In 2 identical randomized, double-blind, placebo-controlled, parallel-group, single-attack studies of adult migraineurs, patients were given the combination of the rapid-release sumatriptan 85 mg plus naproxen sodium 500 mg,

each component used singly, or placebo.¹¹ At 2 hours, the combination regimen was more effective compared with placebo as measured by pain-free and pain-relief rates ($P < 0.001$). In achieving sustained pain-free responses, the combination was more effective than either component or placebo ($P < 0.001$). Sustained therapeutic gain was higher for the combination (16.4%) than for sumatriptan (7.6%) or naproxen (3.7%). Overall, the combination of the fixed-dose reformulated sumatriptan plus naproxen offered improved 24-hour benefits over monotherapy. The sustained pain-free therapeutic gain suggested to the investigators a potential synergistic clinical benefit with the combination regimen.

SUMATRIPTAN, NAPROXEN, AND DEXAMETHASONE—Although the sumatriptan-naproxen studies show that the combination of these 2 drugs can lower the recurrence rate of migraine, some patients who take the combination still have persistent attacks. Intravenous (IV) dexamethasone has been reported anecdotally to be useful in the treatment of migraine and status migrainosus.¹² A small study was conducted in patients who had a history of migraine recurrence, defined as returning of pain within 2 to 24 hours following the single use of sumatriptan 100 mg, zolmitriptan 2.5 mg, or rizatriptan 10 mg in at least 5 consecutive attacks and a reduction in recurrence rate less than 21% following the combination of tolfenamic acid 200 mg or rofecoxib 25 mg in addition to their triptan regimen.¹³ Each of the 20 patients who completed the study presented with frequent recurrence

(that is, recurrence following 60% or more of their migraine attacks). The patients treated 6 consecutive migraine attacks with their usual triptan and NSAID regimen plus dexamethasone 4 mg, taken simultaneously, a maximum of 2 times per week. The results showed that 2 patients experienced recurrence in 50% of 6 attacks, while the remaining 18 patients experienced recurrence in 1 or 2 dexamethasone-treated attacks (mean 23.4%; $P < 0.001$). The investigators stated that the cautious use of oral dexamethasone may be useful for a limited population of migraine patients presenting with recurrence following the combination of a triptan and an NSAID. However, larger studies with a randomized, double-blind design are necessary to confirm these observations.

RIZATRIPTAN AND ROFECOXIB—Rizatriptan has proved to be highly effective in migraine. In a placebo-controlled, outpatient study, the percentage of patients with pain relief at 2 hours postdose was significantly higher after rizatriptan 5 mg (62%) or 10 mg (71%), compared with placebo (35%).¹⁴

Rofecoxib is an NSAID that selectively inhibits cyclooxygenase-2 (COX-2) and has a relatively long half-life of approximately 17 hours,¹⁵ which potentially makes it valuable in preventing migraine recurrence. In an open-label pilot study, 56 triptan-naïve migraineurs were randomized with instructions to take either rizatriptan 10 mg or rizatriptan 10 mg plus rofecoxib 25 mg for 3 consecutive moderate or severe attacks.¹⁶ While no statistically significant difference in absence of headache was

observed at 1, 2, or 4 hours postdose, recurrence (based on all attacks of those patients who achieved pain relief at 4 hours) was observed in 53% of the attacks in the rizatriptan-only group but only 20% in the combination group ($P < 0.001$). Double-blind, placebo-controlled trials are warranted to confirm these results.

ZOLMITRIPTAN VERSUS ASPIRIN PLUS METOCLOPRAMIDE—Oral zolmitriptan has proved to be effective in double-blind, placebo-controlled trials, with the 2.5-mg dose demonstrating an optimal balance between efficacy and tolerability as initial therapy for acute treatment of migraine.¹⁷ Aspirin is also considered useful in treating acute attacks of migraine.³ Metoclopramide is an antiemetic that has the additional advantage of increasing gastrointestinal motility and, hence, absorption of simultaneously ingested medication, a process which might otherwise be hampered by vomiting or gastric stasis during an attack.¹⁸ A double-blind, randomized study was performed that compared zolmitriptan 2.5 mg with a combination of aspirin 900 mg and metoclopramide 10 mg as acute therapy for 3 migraine attacks.¹⁸ The percentage of patients with a 2-hour headache response after the first dose for all 3 attacks was 33.4% with zolmitriptan and 32.9% with aspirin plus metoclopramide ($P = 0.72$). However, the overall 2-hour pain-free response rate was higher for the zolmitriptan group than for the aspirin-metoclopramide regimen (34.6% versus 27.9%; OR = 1.40; 95% CI, 1.09-1.78; $P = 0.007$). Adverse events were reported by 40.8% of

zolmitriptan-treated patients and 29.1% of those treated with aspirin plus metoclopramide, although the discontinuation rate was very low. In this study, zolmitriptan was at least as effective as the comparator regimen in terms of achieving a 2-hour headache response, making both therapies viable options for patients with acute migraine.

SUMATRIPTAN AND METOCLOPRAMIDE—IV metoclopramide administered aggressively—that is, given up to 4 times over 2 hours as needed for persistent severe headaches that present in an emergency room environment—has been shown to be as effective at 2 and 24 hours as subcutaneous sumatriptan 6 mg in the same setting.¹⁹ In a double-blind, crossover study involving 16 triptan-nonresponsive migraineurs, patients were randomized to receive oral sumatriptan 50 mg plus oral metoclopramide 10 mg or oral sumatriptan 50 mg plus placebo and were instructed to medicate themselves when pain was moderate or severe in intensity.²⁰ Meaningful relief was experienced in 10 (63%) of 16 migraines treated with the combination regimen, compared with 5 (31%) of 16 migraines treated with sumatriptan alone. Headache response at 2 hours was achieved in 7 (44%) of 16 migraines with the combination, compared with 5 (31%) of 16 migraines treated with sumatriptan alone. Thus, combining sumatriptan with metoclopramide provided relief in patients who failed to achieve pain remission with triptan monotherapy. However, more studies need to be done to assess whether using a higher dose of sumatriptan and/or initiating

therapy earlier in the acute phase would have provided additional or more rapid relief.

Other agents used in combination

INDOMETHACIN, PROCHLORPERAZINE, AND CAFFEINE—Most migraineurs who seek medical care develop cutaneous allodynia during the course of the attack, a sensory abnormality mediated by sensitization of central trigeminovascular neurons in the spinal trigeminal nucleus.²¹ Treatment with triptans can relieve pain in allodynic migraineurs within a narrow time frame—20 to 120 minutes—that begins with pain onset and ends with the establishment of central sensitization. Indomethacin-responsive headache syndromes are a unique group of primary headache disorders characterized by a prompt and often complete response to indomethacin, an ability not shared by other NSAIDs nor medications usually effective in treating other primary headache disorders.²² Such migraine-like disorders include a select group of trigeminal-autonomic cephalgias, valsalva-induced headaches, and primary stabbing headache (ice-pick headache or jabs-and-jolts syndrome).²² Indomethacin, alone and in combination with prochlorperazine, a phenothiazine antipsychotic and antiemetic that has been used in the treatment of acute severe headache,²³ and caffeine, a vasodilator, has been shown to abolish peripheral and central sensitization in migraine in vivo models.²⁴

In a multicenter, randomized, crossover trial of 112 migraineurs, patients were instructed to treat 2 attacks with a rectal

indomethacin-prochlorperazine-caffeine formulation and 2 attacks with rectal sumatriptan and to record the results.²⁵ The results showed greater pain relief at 2 hours in the combination group than in the triptan group (49% versus 34%; $P < 0.01$). Compared with the sumatriptan alone, the combination was statistically superior in time to a pain-free response (that is, it resulted in a higher percentage of attacks that became pain free from 0.5 hours postdose to 5 hours postdose) and in sustained pain-free response (that is, it resulted in a higher percentage of attacks that became pain free at 2 hours postdose without use of rescue medication or relapses within 48 hours). The combination also alleviated nausea more effectively. No commercially available combination suppository of this type is available in the United States, but a compounding pharmacy can formulate one upon a physician's prescription order.

TRAMADOL AND ACETAMINOPHEN—Tramadol is a centrally acting synthetic opioid analgesic that, when given intramuscularly, has been found to be an effective and reliable alternative treatment option for acute migraine attacks that present in an emergency room setting.²⁶ A randomized, placebo-controlled trial assessed the combination of oral tramadol 75 mg and acetaminophen 650 mg for the treatment of acute migraine pain.²⁷ Treatment response was higher for the dual-drug regimen than for placebo at 2 hours postdose (55.8% versus 33.8%; $P < 0.001$) and at every other assessment from 30 minutes (12.3% versus 6.6%) through

6 hours (64.9% versus 37.7%) (all $P \leq 0.022$). Patients in the active-drug group were more likely than those in the placebo group to experience relief of pain at 2 hours (22.1% versus 9.3%), 6 hours (42.9% versus 25.2%), and 24 hours (52.7% versus 37.9%) (all $P \leq 0.007$). Regarding associated symptoms, fewer patients taking the tramadol-acetaminophen combination experienced moderate to severe photophobia ($P = 0.003$) and moderate to severe phonophobia ($P = 0.008$), but rates of migraine-associated nausea were similar. The combination may be a viable treatment option for patients who experience migraine with minimal nausea or those who have contraindications to migraine-specific therapies.

DOMPERIDONE AND ACETAMINOPHEN—Domperidone has antiemetic properties. Studies on acetaminophen alone as an anti-migraine agent are mixed regarding efficacy.^{28,29} A study compared the effectiveness and tolerability of a fixed combination of domperidone and paracetamol with sumatriptan 50 mg in moderate to severe migraine.³⁰ To do this, 120 patients were recruited from 23 primary care practices throughout the United Kingdom. Patients were randomized to one of the comparator regimens (used to treat their first migraine attack) and then switched to the alternative treatment for their second attack. The 2 treatments were comparable in efficacy ($\leq 15\%$ difference) in relieving headache and reducing nausea and vomiting at 2 hours and 4 hours postdose, and both were well tolerated with no serious adverse effects.

Conclusions

The clinical evidence reviewed here attests to the potential for combining various medications to manage migraine headache, much in the same way multi-drug regimens are used to treat other medical diseases and disorders, including cancer, asthma, diabetes, hypertension, and HIV infection. Because migraine is pathophysiologically complex, the concept of rational combination therapy deserves additional study. Finding the optimal drug combinations (possibly including future, in-the-pipeline products), timing their administration with regard to phase of migraine episode, and balancing an effective dose while minimizing side effects are the challenges faced as more studies are designed and performed. The most promising combinations thus far appear to be the triptan-NSAID regimens that have been studied in double-blind, placebo-controlled trials and that appear to offer improved 24-hour benefits over monotherapy. ■

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CME POST-TEST

Targeting Multiple Mechanisms: New Advances in Migraine Treatment

1. Neuronal membrane channelopathies, mitochondrial dysfunction, and low concentrations of cellular or circulating _____ may play a role in the neuronal hyperexcitability associated with migraine.
 - A. Calcium
 - B. Magnesium
 - C. Phosphorous
 - D. Sodium
2. Of the following statements regarding cortical spreading depression (CDS), which one is NOT a proposed hypothesis?
 - A. CDS initiates the release of neuroactive substances.
 - B. CDS manifests as a rapidly spreading wave of neuronal hyperpolarization.
 - C. CDS occurs in “silent” brain areas in cases of migraine without aura.
 - D. CDS occurs in visual and sensory cortical areas in cases of migraine with aura.
3. Cutaneous allodynia, the clinical phenomena in which normally innocuous tasks such as facial grooming are painful during migraine attacks, is mediated via _____.
 - A. Central sensitization
 - B. Peripheral sensitization
4. Which of the following phrases describes an action of triptans and ergots that may be important to inhibiting migraine?
 - A. Inhibition of neurogenic inflammation
 - B. Propagation of peripheral neurotransmission in the trigeminal nucleus caudalis
 - C. Vasoconstriction of meningeal vessels
 - D. All of the above
5. All of the following are advantages associated with orally dissolving wafer formulations EXCEPT
 - A. They can be taken without water.
 - B. They can be administered conveniently and discretely.
 - C. They may be well suited for treating migraine associated with nausea and vomiting.
 - D. They provide faster relief than conventional tablets.
6. TRUE or FALSE. Opioids are recommended as first-line treatment for migraine.
 - A. True
 - B. False
7. Regarding the combination of a triptan and an NSAID, coadministration of sumatriptan and naproxen appears to slow the _____ of naproxen.
 - A. Absorption
 - B. Metabolism
 - C. Elimination
 - D. Excretion
8. With regard to combining caffeine with an analgesic, a potential pharmacodynamic interaction may be based on the ability of caffeine to block _____ receptors.
 - A. Adenosine
 - B. CGRP
 - C. Dopamine D₂
 - D. 5-HT
9. In 2 recent randomized, controlled trials measuring the performance of a sumatriptan-naproxen combination product,
 - A. The combination was more effective than placebo based on pain-free and pain relief rates at 2 hours.
 - B. The combination was more effective than placebo or either component based on sustained pain-free rates.
 - C. The combination was more effective than either component based on sustained therapeutic gain.
 - D. All of the above are correct.
10. An open-label pilot study published in 2002 by Krymchantowski and colleagues showed that coadministered rizatriptan and rofecoxib was superior with regard to _____ than rizatriptan alone.
 - A. 2-hour pain-free rates
 - B. 24-hour pain-free rates
 - C. Recurrence rates
 - D. Occurrence of GI upset

CME Reply Form

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|------------------------|------------------------|
| 1. A B C D | 6. A B |
| 2. A B C D | 7. A B C D |
| 3. A B | 8. A B C D |
| 4. A B C D | 9. A B C D |
| 5. A B C D | 10. A B C D |

Evaluation

(Required)

Please evaluate this CME activity by circling your response.

1. How do you rate this activity in enabling participants to achieve the stated learning objectives?

- a. Identify specific mechanisms that underlie the pathogenesis of migraine.

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

- b. Describe the benefits and challenges associated with use of monotherapy to abort migraine attacks.

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

- c. Explain how using therapy to target multiple mechanisms in migraine can improve patient outcome.

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

2. How do you rate the content with respect to clinical relevance?

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

3. How do you rate this format for presenting the information?

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

4. Will the information presented change the way you practice?

Yes No Not Sure

5. Do you feel the content was fair, balanced, and free of commercial bias?

Yes No Not Sure

6. What other topics related to migraine care are of interest to you?

7. Additional Comments:

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