Acute treatment of migraine in adults

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INTRODUCTION

Migraine is a common episodic disorder, the hallmark of which is a disabling headache generally associated with nausea and/or light and sound sensitivity. The acute treatment of migraine in adults is reviewed here. Preventive treatment of migraine in adults is discussed separately. (See "Preventive treatment of episodic migraine in adults".)

The pathophysiology, clinical manifestations, and diagnosis of the migraine are also discussed separately. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

APPROACH TO TREATMENT

The abortive (symptomatic) therapy of migraine ranges from the use of simple analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans, antiemetics, calcitonin gene-related peptide (CGRP) antagonists, lasmiditan, and dihydroergotamine. The selection of a specific agent depends on patient-specific factors including the severity and character of symptoms, comorbid conditions, and prior response to treatment (algorithm 1). Noninvasive neuromodulation devices are typically used for patients who do not respond to or tolerate drug treatments and those who wish to avoid medications.

Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses. For some

patients, oral agents are less effective because of poor absorption secondary to migraine-induced gastric stasis and vomiting.

General recommendations for the treatment of acute migraine include the following [1-3]:

- Educate migraine sufferers about their condition and its treatment and encourage them to participate in their own management.
- Use migraine-specific agents (eg, triptans, CGRP antagonists, lasmiditan, dihydroergotamine) for patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics.
- Select a nonoral route of administration for patients whose migraines present early with significant nausea or vomiting.
- Consider a self-administered rescue medication for patients with severe migraines that do not respond well to other treatments.
- Guard against medication overuse headache by educating patients about risk and using prophylactic medications in patients with frequent headaches. (See "Medication overuse headache: Etiology, clinical features, and diagnosis" and "Preventive treatment of episodic migraine in adults".)

The early use of migraine-specific medications for severe attacks provided the best outcomes in a randomized controlled trial of 835 adults with migraine that compared these strategies [4]. One group (step care within attacks) received aspirin (800 to 1000 mg) plus metoclopramide (20 mg) as initial therapy for all attacks; patients not responding to treatment after two hours in each attack escalated treatment to zolmitriptan (2.5 mg). A second group (step care across attacks) received initial treatment with aspirin (800 to 1000 mg) plus metoclopramide (10 mg); patients not responding in at least two of the first three attacks switched to zolmitriptan (2.5 mg) for the next three attacks. In a third group (stratified care), patients with mild headaches were treated with aspirin plus metoclopramide, while those with more severe headaches were treated with zolmitriptan. The latter two groups had significantly better outcomes than the first group as measured by headache response and disability time, although patients in the stratified group had the greatest number of adverse events.

The pharmacologic approach to migraine is directed mainly by the severity of the attacks, the presence of associated nausea and vomiting, the treatment setting (outpatient or medical care facility), and patient-specific factors, such as the presence of vascular risk factors and drug preference.

Mild attacks — For mild migraine attacks not associated with vomiting or severe nausea, simple analgesics (NSAIDs, acetaminophen) or combination analgesics are often tried first because they can be effective and are less expensive than migraine-specific agents [5,6]. For attacks unresponsive to analgesics, we add a triptan. The combined use of an NSAID with a triptan appears to be more effective than using either drug class alone. When attacks are associated with severe nausea or vomiting, an oral or rectal antiemetic drug can be used in conjunction with simple or combination analgesics. (See 'Simple analgesics' below and 'Triptans' below and 'Triptans with NSAIDs' below and 'Antiemetics' below.)

Moderate to severe attacks — For moderate to severe migraine attacks not associated with vomiting or severe nausea, oral migraine-specific agents are first-line, including oral triptans and the combination of sumatriptan-naproxen [5,6]. For those with contraindications to or who do not tolerate triptans, a calcitonin gene-related peptide (CGRP) antagonist or lasmiditan may be effective. When complicated by vomiting or severe nausea, severe migraine attacks can be treated with an antiemetic drug or nonoral migraine-specific medications including subcutaneous sumatriptan, nasal sumatriptan and zolmitriptan, parenteral dihydroergotamine, or nasal zavegepant. (See 'Triptans' below and 'Triptans with NSAIDs' below and 'CGRP antagonists' below and 'Lasmiditan' below and 'Antiemetics' below and 'Ergots' below.)

Status migrainosus — For severe intractable migraine attacks, or status migrainosus (ie, a debilitating attack lasting for more than 72 hours), patients may be treated with a combination of intravenous fluids plus parenteral medications such as ketorolac and a dopamine receptor blocker. Other parenteral medications such as valproate and/or dihydroergotamine [7] may also be warranted depending on response to initial therapy [8]. Treatment options are not based on high-quality evidence and medication selection depends upon patient-level factors. (See 'Nonsteroidal anti-inflammatory drugs' below and 'Prochlorperazine' below and 'Metoclopramide' below and 'Others' below and 'Sodium valproate' below.)

Administration of parenteral dexamethasone is often used to prevent attack relapse. (See 'Abortive therapy plus parenteral dexamethasone' below.)

Patients may require admission for persistent disabling symptoms despite the initial treatment regimen or for weaning of medication overuse to monitor for withdrawal symptoms [9-11]. (See 'Emergency settings' below and "Medication overuse headache: Treatment and prognosis", section on 'Outpatient and inpatient settings' and 'Antiemetics' below and 'Simple analgesics' below and 'Ergots' below.)

Variable attacks — Many patients with migraine have attacks that vary in severity, time of onset, and association with vomiting and nausea [12]. These patients may require two or more options for self-management of acute migraine, including oral medications for mild to

moderate attacks and nonoral medications (eg, subcutaneous or nasal triptans) for more severe attacks or those associated with vomiting or severe nausea.

Emergency settings — Patients who present with migraine in emergency settings generally have unusually severe attacks, and in many cases their customary acute migraine treatment has failed to provide relief [13]. The treatment of migraine attacks in the emergency department or other urgent care settings follows the same principles as treatment in nonurgent settings outlined above (see 'Mild attacks' above and 'Moderate to severe attacks' above), with the obvious difference that parenteral medications are more readily available. The following are reasonable options, with evidence of efficacy from randomized trials [13-20]:

- Sumatriptan 6 mg subcutaneous injection (see 'Triptans' below)
- Antiemetics-dopamine receptor blockers (see 'Antiemetics' below):
  - Prochlorperazine 10 mg intravenous (IV) or intramuscular (IM)
  - Metoclopramide 10 mg IV
  - Chlorpromazine 0.1 mg/kg (or 12.5 mg) single dose as a slow IV infusion (maximum rate 1 mg/minute); maximum cumulative dose 25 mg
- Dihydroergotamine (1 mg IV) combined with metoclopramide (10 mg IV) (see 'Dihydroergotamine' below)
- Ketorolac 30 mg IV or 60 mg IM (lower doses may be warranted for patients ≥65 years old, <50 kg body weight, and those with kidney impairment) (see 'Nonsteroidal anti-inflammatory drugs' below)

For patients who present to the hospital emergency department with severe migraine, particularly if the migraine is accompanied by severe nausea or vomiting, we suggest initial treatment with either subcutaneous sumatriptan and/or a parenteral antiemetic (eg, prochlorperazine, metoclopramide, chlorpromazine) at the doses listed above. When giving parenteral antiemetics for migraine, we suggest adjunct use of diphenhydramine (12.5 to 25 mg IV every hour up to two doses) to prevent akathisia and other dystonic reactions. (See 'Antiemetics' below.)

Dihydroergotamine (DHE 45) 1 mg IV combined with metoclopramide 10 mg IV is also a reasonable alternative for treatment of intractable severe migraine in the emergency department, and it can be used if metoclopramide monotherapy is ineffective. Parenteral dihydroergotamine should not be used as monotherapy. Dihydroergotamine is contraindicated in patients with ischemic vascular disease involving cardiac, cerebrovascular, or peripheral circulations. (See 'Dihydroergotamine' below.)

For patients who are treated in the emergency department or clinic for migraine headache with one of the standard migraine abortive therapies, we suggest adjunctive treatment with dexamethasone to reduce the risk of early headache recurrence. (See 'Abortive therapy plus parenteral dexamethasone' below.)

Overuse of opioid medications for acute headache in hospital emergency departments appears to be widespread in the United States and Canada [21,22], despite available practice guidelines that recommend nonopioid medications as first-line therapy for severe migraine [2], or recommend that opioids should not be used in the acute treatment of migraine [23,24]. Patients treated with opioids as first-line therapy are significantly more likely to return to the emergency department with a headache within seven days of the original visit [21,25].

Pregnancy — The treatment of migraine in pregnant patients differs somewhat from the treatment of others because of concerns about adverse fetal drug effects. This aspect of acute migraine care is reviewed separately. (See "Headache during pregnancy and postpartum", section on 'Acute migraine treatment'.)

Avoidance of medication overuse — Medication overuse headache (MOH), also called analgesic rebound headache, is a common disorder with significant morbidity. Many symptomatic medications used to treat headaches have the potential for causing MOH. However, the degree of risk differs depending upon the specific medication or class of medications. Based upon the literature and clinical experience, the risk for MOH appears to be highest with opioids, butalbital-containing combination analgesics, and aspirin-acetaminophen-caffeine combinations. The risk with triptans is considered intermediate by some experts but high by others. MOH may be avoided with some CGRP antagonists, which are effective for preventive as well as acute treatment of migraine [26-28]. The risk is lowest with NSAIDs, which may even be protective against the development of chronic migraine for patients who have less than 10 headache days per month. (See "Medication overuse headache: Etiology, clinical features, and diagnosis", section on 'Causal medications'.)

In order to prevent the development of MOH, most acute medications should be limited to less than 10 days per month (or less than 15 days per month for aspirin, acetaminophen, and NSAIDS), and preventive therapies should be used as the mainstay in patients with frequent headaches. (See "Medication overuse headache: Etiology, clinical features, and diagnosis".)

SIMPLE ANALGESICS

Some patients with migraine have an optimal response with simple analgesics, including aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen (table 1) [20].

Nonsteroidal anti-inflammatory drugs — NSAIDs with reported efficacy in randomized placebo-controlled trials of migraine therapy include aspirin (900 to 1000 mg) [29,30], ibuprofen (400 to 600 mg) [31], naproxen sodium (275 to 825 mg) [32], diclofenac (50 to 100 mg) [33], diclofenac epolamine (65 mg) [34], tolfenamic acid (200 mg) [35], celecoxib [36], and dexketoprofen (50 mg) [37,38]. Some of these studies are limited by varying outcome measures and definitions of migraine.

A 2013 systematic review of eight randomized trials found that parenteral ketorolac (30 mg intravenous [IV] or 60 mg intramuscular [IM]) was effective for acute migraine in comparison with other agents, including intranasal sumatriptan, IV prochlorperazine, IV chlorpromazine, and IV dihydroergotamine combined with metoclopramide [39].

One trial showed powdered diclofenac potassium (50 mg) produced more rapid and effective pain relief at two hours than tablets [40].

Although the data are limited, benefit may be seen with indomethacin as abortive therapy for migraine. It is a potent NSAID that is also available in suppository form, which may be helpful for nauseated patients. Indomethacin suppositories contain 50 mg of the drug; the suppositories may be cut into halves or thirds for patients with recurrent attacks.

There are no studies comparing the relative efficacy of different NSAIDs. If one NSAID is ineffective, a different drug may be tried. (See "NSAIDs: Therapeutic use and variability of response in adults".)

Acetaminophen — Acetaminophen is an effective abortive agent in some patients [41]. This was illustrated in a population-based randomized placebo-controlled trial of 289 patients with self-reported migraine, which found acetaminophen at a dose of 1000 mg to be highly effective for treating pain, functional disability, photophobia, and phonophobia, although the study excluded patients with severe symptoms requiring bed rest or associated with vomiting more than 20 percent of the time [42].

Acetaminophen can be used in combination with NSAIDs. The combination of acetaminophen-aspirin-caffeine was found to alleviate headaches in patients with uncomplicated migraine in one report [43].

TRIPTANS

The serotonin 1b/1d agonists (triptans) are effective for the acute treatment of migraine [20]. The triptans were developed specifically to treat migraine [1,2]. However, triptan responsiveness should not be considered diagnostic of migraine, as other primary headaches and secondary headaches may also improve with triptan treatment [44]. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

All of the triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem [45]. Triptans inhibit transmission in the trigeminal nucleus caudalis, thereby blocking afferent input to second order neurons; this effect is probably mediated by reducing the levels of calcitonin gene-related peptide (CGRP). (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

Triptans may also activate 5-HT 1b/1d receptors in descending brainstem pain-modulating pathways and thereby inhibit dural nociception [46].

Preparations and efficacy — The available triptans include sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. Sumatriptan can be given as a subcutaneous injection (usually administered by autoinjector in the thigh), as a nasal spray, as a nasal powder, or orally. Zolmitriptan is also available for both nasal and oral use. The others are available for oral use only, including as pills and orally disintegrating tablets and/or films (table 2).

A number of randomized controlled trials and systematic reviews have found all of the triptans to be effective for the treatment of acute migraine [47]. The range of findings is illustrated by the following reports:

- **Eletriptan** – In a meta-analysis of six randomized controlled trials of eletriptan involving 3224 patients, eletriptan at doses of 20, 40, and 80 mg was significantly better than placebo for all main outcomes (including headache response at one and two hours and sustained relief over 24 hours) [48]. Pain relief was dose-dependent, although the differences in most efficacy outcomes between the 40 and 80 mg doses were not statistically significant. The drug was well tolerated and caused no major harm. The incidence of minor side effects was also dose related, but all adverse effects were transient and reversible. Eletriptan is not available in 80 mg tablets in the United States, and 40 mg is recommended for most patients [49].

- **Naratriptan** – At least three randomized trials have found that naratriptan significantly improves acute migraine relief compared with placebo [50-52]. In one of the studies, a dose of 2.5 mg was most effective in producing headache relief at four hours, with an adverse event rate similar to placebo [51]. Adverse events did not appear to be dose related.

  In a second study, patients who did not respond to sumatriptan 50 mg with a first attack had a significantly superior response to naratriptan 2.5 mg compared with placebo during a second migraine attack one week later, suggesting that patients who do not respond to one triptan may respond to another [52]. One problem with this study is that the 50 mg dose of sumatriptan used is often suboptimal [53]. On the other hand, it is worthwhile to try another triptan if the response is not optimal.

- **Rizatriptan** – The efficacy of rizatriptan for acute migraine has been demonstrated in a systematic review of multiple randomized placebo-controlled studies [54]. Significant benefit of rizatriptan compared with placebo was shown for both the 5 and 10 mg dose of rizatriptan for all five main efficacy outcomes (ranging from relief at 1 to 24 hours). The 10 mg dose was more effective than 5 mg. The most common adverse effects were dizziness, asthenia/fatigue, nausea, and somnolence; in one study these effects were dose dependent.

- **Sumatriptan** – The subcutaneous, oral, and intranasal preparations of sumatriptan have proven efficacy in randomized placebo-controlled trials of acute migraine therapy, as established in systematic reviews and meta-analyses [55-58].

  - **Oral sumatriptan** is given at 50 to 100 mg once. The most effective dose of oral sumatriptan is 100 mg, while the 50 mg dose may provide the best combination of efficacy and tolerability [58,59]. The dose (same strength as the initial dose) may be repeated once after two hours if needed. The maximum dose is 200 mg per 24 hours.

  - **Subcutaneous sumatriptan** (6 mg) is more effective than oral sumatriptan, but its use is associated with more adverse events [60]. Subcutaneous sumatriptan has the fastest onset of action. For acute migraine, the usual initial dose of subcutaneous sumatriptan is 6 mg. The dose may be repeated once if needed after one hour. For patients who are intolerant of the 6 mg dose but need a parental formulation (eg, due to protracted vomiting with migraine), some experts try a lower initial/repeat dose (eg, 3 or 4 mg) [61]. Sumatriptan for injection is commercially available in 3, 4, and 6 mg formulations. The recommended maximum is 6 mg per dose and 12 mg per 24 hours. In one trial of subcutaneous sumatriptan in 639 patients, administration of a second dose of the drug 60 minutes after the first in those who did not respond well initially provided little additional benefit [62]. Common side effects of subcutaneous sumatriptan include an injection site reaction, chest pressure or heaviness, flushing, weakness, drowsiness, dizziness, malaise, a feeling of warmth, and paresthesias. Most of these reactions occur soon after the injection and resolve spontaneously within 30 minutes.

  - **Intranasal spray sumatriptan** (liquid) is given as one insufflation of 20 mg in a single nostril. The dose may be repeated once after two hours if needed. The maximum dose is 40 mg per 24 hours. Intranasal sumatriptan has fewer side effects than the injectable formulation [60]. The most common side effect of intranasal sumatriptan is an unpleasant taste.

  - **Intranasal sumatriptan coformulated with DDM** (a permeation enhancer for more rapid absorption into the systemic circulation) is given as a single insufflation

of 10 mg in one nostril [63]. The maximum dose is 30 mg per 24 hours with individual doses separated by at least one hour. The most common adverse reactions related to application were nasal discomfort, unpleasant taste, and throat irritation.

- **Nasal powder sumatriptan** is given as a 22 mg dose using one 11 mg capsule insufflated in each nostril with a breath-powered delivery device. The dose may be repeated once after two hours if needed. The maximum dose is 44 mg per 24 hours. The most common adverse reactions are an abnormal or unpleasant taste and nasal discomfort.

- **Zolmitriptan** – A number of randomized placebo-controlled trials and a systematic review and meta-analysis [64] have proven the efficacy of zolmitriptan as acute migraine therapy. As an example, one trial of 1000 patients with migraine compared four doses of zolmitriptan (1, 2.5, 5, and 10 mg) with placebo [65]. There was a dose-response relationship in terms of both efficacy and adverse effects; 2.5 mg appeared to be the optimal starting dose. The most common side effects included nausea, dizziness, somnolence, paresthesia, fatigue, and tightness in the throat or chest. The incidence of unpleasant taste is lower with intranasal zolmitriptan, as compared with that reported in trials of intranasal sumatriptan.

Choice of triptan — The choice of a triptan should be individualized; different pharmacologic properties and delivery routes may help guide the choice (table 2). Patients who do not respond well to one triptan may respond to another [66].

Relatively few trials have compared the triptans head-to-head, making it difficult to decide whether to use one versus another. A meta-analysis of 53 clinical trials of the oral serotonin agonists that included over 24,000 patients concluded that all of the available oral drugs are effective and well tolerated [67]. The highest likelihood of consistent success was found with rizatriptan (10 mg), eletriptan (80 mg), and almotriptan (12.5 mg). The findings of a subsequent network meta-analysis suggested that eletriptan was the most likely of all the triptans to produce short-term and sustained benefit [68]. These data and clinical experience suggest that sumatriptan, rizatriptan, eletriptan, almotriptan, and zolmitriptan are very similar orally, while naratriptan and frovatriptan are slower in onset and have lower efficacy.

Sumatriptan offers the most options for routes of drug delivery, with subcutaneous sumatriptan offering the fastest onset of action. The dose of rizatriptan must be adjusted downward in patients who take propranolol, since propranolol increases rizatriptan levels by 70 percent. Naratriptan and frovatriptan have the slowest onset of action among the triptans and may have the lowest propensity to cause side effects [69].

Factors predicting response — Prompt treatment of migraine attacks is considered important to successful acute therapy [53,70,71], but few rigorous studies have examined the factors that may influence the probability of a good response to triptan therapy.

- In a randomized placebo-controlled trial that evaluated 403 patients with migraine, almotriptan 12.5 mg was effective whether started when headache was early and mild, or started when headache was moderate to severe [72]. When treatment was initiated while headache intensity was mild and within one hour of onset, a significantly greater proportion of patients were pain-free at two hours with almotriptan than with placebo (49 versus 25 percent) [72]. Similarly, when treatment was started when headache intensity was moderate to severe, almotriptan remained significantly better than placebo on the same outcome measure (40 versus 15 percent).

- Another study analyzed a database of 130,000 migraine attacks in 28,000 patients with migraine [73]. Pretreatment pain severity was the strongest predictor of both headache relief (defined as mild or no pain) and pain-free response two hours after taking sumatriptan, with lower baseline severity predicting a better response. The resistance of severe pain to triptan therapy found in this study may be due to the development of central sensitization during the attack, which is thought to counteract analgesic and triptan therapy. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

In patients susceptible to cutaneous allodynia (the perception of pain produced by innocuous stimulation of normal skin), limited data suggest that triptans are less effective once allodynia is established during migraine attacks. In a study of 31 patients, triptan treatment resulted in complete pain relief by two hours in only 15 percent of 34 allodynic attacks versus 97 percent of 27 nonallodynic attacks [74]. The authors concluded that patients who develop allodynia, which takes one to four hours to establish [75], should take triptans as early as possible in a migraine attack. Conversely, patients who never develop allodynia can benefit from triptan therapy at any time during an attack. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

Limitations to use — Triptans have proven to be safe and effective for most patients with migraine [76]. A systematic review of observational studies found no association between triptan use and the risk of vasoocclusive cardiovascular events, though only four relevant studies were identified [77]. Similarly, in a cohort study of 63,575 patients with migraine, 13,664 of whom were treated with a triptan, there was no association between triptan prescription and stroke, other cardiovascular events, or death [78]. However, in this cohort, triptans were prescribed to those at less risk of these events.

All triptans should be limited to no more than 10 days of use per month to avoid medication overuse headache. Based on limited evidence, it is still recommended that triptans be

avoided in patients with hemiplegic migraine, basilar migraine, ischemic stroke, ischemic heart disease, Prinzmetal's angina, and uncontrolled hypertension [79].

Combination with monoamine oxidase inhibitors is relatively contraindicated with triptans because of the risk of serotonin syndrome. Triptans should not be used within 24 hours of the use of ergotamine preparations or a different triptan medication [80]. (See "Serotonin syndrome (serotonin toxicity)".)

Eletriptan is primarily metabolized by cytochrome P-450 enzyme CYP3A4. Therefore, eletriptan should not be used within at least 72 hours of treatment with other drugs that are potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir.

Concerns have been raised about the development of a serotonin syndrome (see "Serotonin syndrome (serotonin toxicity)") in patients who use triptans in combination with a selective serotonin reuptake inhibitor (SSRI) or a selective serotonin-norepinephrine reuptake inhibitor (SNRI) [81]. However, the added risk of serotonin syndrome posed by the combined use of a triptan with an SSRI or SNRI appears to be very low to nonexistent [82-85]. Thus, many headache experts suggest that triptans in combination with SSRIs or SNRIs can be used in most cases where both are needed as long as the risks and benefits are discussed, and patients are monitored for symptoms of serotonin syndrome. The combination should be discontinued if such symptoms arise.

TRIPTANS WITH NSAIDS

The combined use of a triptan and a nonsteroidal anti-inflammatory drug (NSAID) to treat acute migraine appears to be more effective than using either drug class alone. The best-studied combination is sumatriptan with naproxen. A systematic review and meta-analysis, updated in 2016, found that the combination of sumatriptan and naproxen was more effective than either agent alone for the treatment of acute migraine headache [86]. Among the largest of the included studies were two randomized placebo-controlled trials of similar design, involving a total of nearly 3000 patients, which evaluated a formulation of sumatriptan succinate 85 mg and naproxen sodium 500 mg in a single tablet (Treximet) [87]. The following observations were reported:

- At two hours after dosing, the combination of sumatriptan and naproxen was more effective than placebo or sumatriptan alone for headache relief (defined as reduction of pain from moderate or severe intensity to mild intensity or no pain without use of rescue medication)

- Sumatriptan and naproxen was more effective than sumatriptan monotherapy and naproxen monotherapy for sustained pain-free response (defined as initially moderate or severe pain reduced to no pain from 2 through 24 hours after dosing without use of rescue medication)

- The combined agent was well tolerated; dizziness, somnolence, paresthesia, and nausea were the most common side effects

In two randomized placebo-controlled trials with more than 1000 patients that tested early treatment (within one hour of migraine onset when the pain was mild), a pain-free response at two hours was significantly more frequent in patients assigned to the combination sumatriptan and naproxen 85/500 mg (approximately 50 percent, versus approximately 16 percent with placebo) [88]. Even at 30 minutes, there was a statistically significant pain-free response with combination sumatriptan plus naproxen.

Whether the results of the trials testing sumatriptan with naproxen are generalizable to other triptan/NSAID combinations is uncertain. However, a double-blind controlled trial of 279 patients found that the combination of frovatriptan (2.5 mg) and dexketoprofen (25 mg or 37.5 mg) was more effective than frovatriptan alone for treating migraine attacks, as measured by the proportion of subjects who were pain-free at two hours (51 percent for frovatriptan with either dose of dexketoprofen, versus 29 percent for frovatriptan alone) [89].

ANTIEMETICS

Intravenous (IV) metoclopramide and IV or intramuscular (IM) prochlorperazine can be used along with other agents or as monotherapy for acute migraine headache. These medications act as antiemetics mainly because they are dopamine receptor antagonists. In addition, they are effective for reducing migraine headache pain. The benefit of these agents for migraine has been demonstrated in randomized placebo-controlled trials as will be discussed below. Intravenous diphenhydramine (12.5 to 25 mg every hour for two hours) is sometimes given with these drugs to prevent akathisia and acute dystonic reactions, which are the main side effects of this class of medications.

Other antiemetic medications can cause dose-dependent prolongation of the QT interval on electrocardiogram (ECG), which can lead to a life-threatening cardiac arrhythmia, including torsades de pointes. These include haloperidol, chlorpromazine, droperidol, and ondansetron. They may be used for patients when migraine symptoms are unresponsive to antiemetics that do not prolong the QT interval. They should be avoided in patients with congenital long QT syndrome, those with persistent corrected QT interval (QTc) >500 milliseconds on ECG, and with other risk factors for acquired long QT syndrome (table 3).

(See "Acquired long QT syndrome: Definitions, pathophysiology, and causes", section on 'Risk factors for drug-induced long QT syndrome'.)

In contrast with IV or IM preparations, oral antiemetics should not be considered as monotherapy in acute migraine [1,2].

Prochlorperazine — In controlled trials, IV prochlorperazine appears to be as effective or more effective than IV metoclopramide or subcutaneous sumatriptan, and more effective than hydromorphone or placebo in the acute treatment of migraine [14,16,19,90,91]. In most of these trials, diphenhydramine was used as adjunct treatment to prevent akathisia and dystonic reactions, and the possibility of migraine benefit from diphenhydramine cannot be completely discounted.

In one randomized controlled trial evaluated that 127 adults who presented to the emergency department for the treatment of migraine, the combination of IV prochlorperazine (10 mg) and IV diphenhydramine (25 mg) was more effective than IV hydromorphone (1 mg) for achieving sustained headache relief, defined as a reduction to a level of mild or no headache within two hours of medication administration and without relapse or need for rescue mediation for 48 hours [91].

In another double-blind randomized controlled trial that evaluated the emergency department treatment of migraine in 66 patients, the combination of IV prochlorperazine (10 mg) and IV diphenhydramine (12.5 mg) was significantly more effective than subcutaneous sumatriptan (6 mg) for the reduction of pain intensity at 80 minutes or time of discharge [92]. A high dropout rate upon attempted telephone contact at 72 hours precluded meaningful assessment of headache recurrence, although none of the enrolled patients returned to the emergency department with complaint of headache.

Metoclopramide — IV metoclopramide is effective for acute migraine treatment, as demonstrated in systematic reviews and meta-analyses [14,16,19,93]. One meta-analysis, published in 2004, reviewed 13 clinical trials [93]. Study methods varied considerably, and the quality of the included studies was generally poor. The following observations were made [93]:

- In pooled data from three studies, metoclopramide was more likely to provide headache pain reduction than placebo (odds ratio [OR] 2.84; 95% CI 1.05-7.68).
- The NNT to enable one patient to achieve significant reduction in pain with metoclopramide was four.
- Metoclopramide was less effective than chlorpromazine and prochlorperazine in relieving pain and nausea, although differences were not always statistically significant.

- One trial found that metoclopramide treatment was not statistically different than sumatriptan for rates of complete resolution of migraine or significant reduction in pain or nausea.

Oral metoclopramide may be effective when combined with other treatments. (See 'Use in adjunctive therapy' below.)

Others — Chlorpromazine, ondansetron or granisetron, droperidol, and haloperidol appear to be effective for the acute treatment of migraine but are not considered first-line agents because the evidence is mainly from lower-quality randomized trials and because rates of adverse effects are high [19]. Adverse effects with these agents may include rebound headache, akathisia, and arrythmia from QT-segment prolongation on ECG (table 3). If these medications are used, ECG should be obtained at baseline and at two to three hours after dosing [94], and patients should be monitored for clinical symptoms suggestive of QT-segment prolongation. (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management", section on 'Precautions for any patient starting QT-prolonging drugs'.)

- **Chlorpromazine** – Although data are limited, IV chlorpromazine appears to be effective in the acute treatment of migraine [14,16,19]. In one of the larger clinical trials that assessed chlorpromazine treatment in the emergency department, 128 patients with migraine were assigned to chlorpromazine 0.1 mg/kg IV or placebo. Chlorpromazine treatment was associated with significant improvement in pain, nausea, photophobia, phonophobia, and need for rescue medication at 60 minutes compared with placebo [95]. Benefit extended to both migraine with aura and migraine without aura. The number needed to treat (NNT) to enable one patient to achieve significant improvement at 60 minutes was two. In addition, chlorpromazine-treated patients had a significantly reduced rate of headache recurrence at 24 hours. Drowsiness and postural hypotension were seen more frequently with chlorpromazine treatment than with placebo.

- **Ondansetron and granisetron** – Treatment of acute migraine using ondansetron or granisetron has not been rigorously evaluated, although there are reports describing their use [96]. However, both ondansetron and granisetron have been associated with a relatively high incidence of headache as an adverse effect [97-99]. Several guidelines recommend against the use of intravenous granisetron for acute migraine [2,19].

- **Droperidol** – In a randomized controlled trial of over 300 patients, droperidol (2.75 mg, 5.5 mg, and 8.25 mg IM) was superior to placebo for the treatment of acute migraine attacks [100]. However, these doses were associated with high rates of adverse events including akathisia and asthenia. Systematic reviews of randomized controlled trials have found that the effectiveness of parenteral droperidol (IV or IM) for acute migraine relief was equal to or better than prochlorperazine [14,16].

- **Haloperidol** – A placebo-controlled trial of 40 hospitalized patients found that haloperidol (5 mg IV) was effective for migraine pain relief [101]. Adverse effects, mainly sedation and akathisia, occurred in 80 percent of patients who received haloperidol. Another trial randomly assigned 64 adults presenting to the emergency department with acute migraine to treatment with either haloperidol 5 mg IV or metoclopramide 10 mg IV [102]. There was no difference in pain relief between the treatment groups, but the incidence of restlessness (akathisia) was higher in the haloperidol group (43 versus 10 percent).

Use in adjunctive therapy — Antiemetics are commonly used as adjunctive therapy to treat migraine. As an example, nonsteroidal anti-inflammatory drugs (NSAIDs) can be combined with metoclopramide to decrease nausea and vomiting. The efficacy of this approach was illustrated in a randomized trial of 421 patients with migraine that compared oral lysine acetylsalicylate (equivalent to 900 mg of aspirin) plus oral metoclopramide (10 mg) with oral sumatriptan (100 mg) or placebo [103]. Headache intensity decreased in 57, 53, and 24 percent of patients, respectively. Thus, in patients who will not use suppositories, or who are having difficulty tolerating oral analgesics, an analgesic plus metoclopramide is a reasonable, relatively low-cost alternative.

CGRP ANTAGONISTS

Pharmacologic modulation of calcitonin-gene related peptide (CGRP) activity appears to mediate trigeminovascular pain transmission in migraine (see "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults"). Several CGRP antagonists have been developed for acute and preventive treatment of migraine headache. Monoclonal antibodies directed against the CGRP receptor or ligand are given by periodic injection for migraine prevention. Small-molecule CGRP antagonists (also termed "gepants") are oral or intranasal medications with specific agents formulated for acute treatment, and others for migraine prevention.

CGRP antagonists are often used for patients with either insufficient response or contraindication (eg, coronary artery disease) to treatment with triptans and/or antiemetics. Options for acute migraine include:

- **Ubrogepant** – Ubrogepant is given as a single oral tablet at either 50 or 100 mg. The dose may be repeated in two hours with a maximum daily dose of 200 mg.

  Multiple clinical trials have shown ubrogepant is effective for acute migraine [104-106]. One trial randomly assigned adult patients with episodic migraine in a 1:1:1 ratio to one tablet of ubrogepant 100 mg, ubrogepant 50 mg, or placebo taken within four hours of a single migraine attack; an optional second dose or the patient's own rescue

medication was permitted 2 to 48 hours after the first dose [105]. With efficacy data for 1327 patients, the proportion with pain freedom at two hours after treatment was greater for those assigned to the 100 mg and 50 mg doses of ubrogepant compared with placebo (21.2, 19.2, and 11.8 percent, respectively). Also, the proportion who reported absence of their most bothersome migraine-associated symptom (ie, photophobia, phonophobia, or nausea) at two hours after treatment was greater for those assigned to ubrogepant 100 and 50 mg compared with placebo (37.7, 38.6, and 27.8 percent). The most common adverse events were nausea, somnolence, and dry mouth.

Ubrogepant may also be effective at preventing onset of acute headache when taken during migraine prodrome. In a trial of 477 patients with migraine who were treated at onset of prodromal symptoms and prior to headache, the proportion of patients who remained free of moderate to severe headache at 24 hours was higher in patients who received ubrogepant than those who received placebo (46 versus 29 percent) [106]. Enrolled patients had migraines that consisted of prodromal symptoms (eg, photophobia, fatigue, neck pain) occurring one to six hours before headache onset in at least 75 percent of attacks. Adverse rates were low in the trial and included nausea, fatigue, dizziness, and somnolence.

Ubrogepant received US Food and Drug Administration (FDA) approval for the treatment of acute migraine in adults in December 2019 [107].

- **Rimegepant** – Rimegepant is given at 75 mg as a single oral dose.

  Clinical trial evidence supports the efficacy of rimegepant for acute migraine treatment. In a clinical trial of 1466 patients with migraine, patients who received rimegepant were likelier to be pain free at two hours than those who received placebo (21 versus 11 percent) and had higher rates of freedom from most bothersome migraine symptom (35 versus 27 percent) [108]. Nausea and lower urinary tract infections were common adverse effects. Similar results were reported in another trial of 1186 patients with migraine [109]. Rimegepant received US FDA approval for acute migraine treatment in February 2020 [110].

  Rimegepant has also been found to be effective in some patients who did not respond previously to a triptan [111]. Rimegepant is also approved by the US FDA for migraine prevention when given at a dose of 75 mg once every other day. (See "Preventive treatment of episodic migraine in adults", section on 'CGRP antagonists'.)

- **Zavegepant** – Zavegepant is given at 10 mg intranasally as a single spray.

  In a trial of 1405 adult patients with migraine, those assigned to zavegepant 10 mg were likelier to be pain free at two hours than patients assigned to placebo (24 versus

15 percent; risk difference 9 percent, 95% CI 4.5-13.1) [112]. In addition, resolution of the most bothersome acute symptom (eg, photophobia, nausea) was more common with zavegepant (40 versus 31 percent). Adverse events were transient and mild and included dysgeusia and nasal discomfort. Nasal administration of a CGRP-receptor antagonist provides rapid absorption and effect and may be preferred for patients with nausea and/or vomiting who are unable to tolerate oral options. Zavegepant was approved for acute migraine by the US FDA in 2023 [113].

The safety of using a CGRP antagonist within two to four hours of a triptan or ergotamine agent is not well established. Additional long-term data on CGRP antagonists are needed to better define safety and tolerability.

Several other CGRP antagonists are approved for migraine prevention, as discussed separately. (See "Preventive treatment of episodic migraine in adults", section on 'CGRP antagonists'.)

LASMIDITAN

Lasmiditan is a selective serotonin 1F receptor agonist that lacks vasoconstrictor activity and therefore can be used for patients with relative contraindications to triptans due to cardiovascular risk factors [114].

In a randomized trial of over 2200 patients with episodic migraine, the proportion who were headache pain-free at two hours was greater with lasmiditan 200 mg (32 versus 15 percent with placebo; absolute risk difference [ARD] 17 percent; odds ratio [OR] 2.6, 95% CI 2.0-3.6) and lasmiditan 100 mg (28 versus 15 percent; ARD 13 percent; OR 2.2, 95% CI 1.6-3.0) [115]. In a 2021 meta-analysis including five trials and more than 7000 patients, resolution of pain at two hours likelier with lasmiditan than placebo (relative risk [RR] 1.95, 95% CI 1.3-3.0) [116]. Lasmiditan was also effective for treating acute migraine in another randomized placebo-controlled trial of 2310 patients [117].

In October 2019, the US Food and Drug Administration (FDA) approved lasmiditan oral tablets for the acute treatment of migraine in adults [118]. The initial dose of lasmiditan is 50 or 100 mg; there is no benefit with taking a second dose for the same migraine attack. With subsequent attacks, the dose may be increased to 100 or 200 mg as needed, but no more than one dose should be taken in 24 hours [119].

The most common adverse event associated with lasmiditan is dizziness; other relatively frequent adverse events are paresthesia, somnolence, fatigue, and nausea [115,117]. Dizziness with lasmiditan is dose-dependent and largely mild to moderate in severity, with a median duration of 1.5 to 2 hours [120]. The drug may cause driving impairment, and

patients should not drive a motor vehicle, operate machinery, or engage in potentially hazardous activities for at least eight hours after each dose of lasmiditan [119].

ERGOTS

A variety of ergotamine preparations, alone and in combination with caffeine and other analgesics, have been used for the abortive treatment of migraine [121]. Both ergotamine and dihydroergotamine bind to 5HT 1b/d receptors, just as triptans do. As the evidence reviewed below suggests, parenteral dihydroergotamine is effective for acute migraine, while the effectiveness of ergotamine is uncertain.

Dihydroergotamine — Dihydroergotamine is an alpha-adrenergic agonist that is a weaker arterial vasoconstrictor and more potent venoconstrictor than ergotamine tartrate. It is also a potent 5-HT 1b/1d receptor agonist. Dihydroergotamine has fewer side effects than ergotamine [7]. It is available for intravenous (IV), intramuscular (IM), subcutaneous, and intranasal use. Dihydroergotamine is often used in combination with an antiemetic drug, and this is always the case when it is given by intravenous administration.

The use of intravenous dihydroergotamine for the treatment of chronic intractable migraine headache or status migrainosus (a debilitating migraine attack lasting for >72 hours) is discussed separately. (See "Medication overuse headache: Treatment and prognosis", section on 'Dihydroergotamine'.)

Parenteral dihydroergotamine (DHE 45) administered with an antiemetic appears to be effective for acute migraine. This conclusion is supported by the findings of a systematic review that analyzed 11 randomized controlled trials of IV or IM dihydroergotamine therapy for acute migraine in adults [122]. The quality of the included studies was variable, and most had relatively small sample sizes. The following observations were reported:

- In two studies, dihydroergotamine alone (without an antiemetic) was less effective on most outcome measures than sumatriptan [123,124], and in one study was less effective on some (but not all) outcome measures than chlorpromazine [125].

- In eight studies, the combination of parenteral dihydroergotamine with an antiemetic (most commonly metoclopramide) was as effective as or more effective than meperidine, valproate, or ketorolac in relieving migraine headache and preventing relapses.

Whether dihydroergotamine contributed additional benefit when used with an antiemetic in these studies is uncertain, since the antiemetic metoclopramide is known to be effective for migraine when used alone (see 'Metoclopramide' above). However, in several studies dihydroergotamine combined with an antiemetic was superior to other agents combined

with the same antiemetic, suggesting that dihydroergotamine does have independent efficacy for migraine [125].

Self-administered intranasal dihydroergotamine has been found, in placebo-controlled trials, to be efficacious for the treatment of migraine symptoms [126,127]. In one trial of over 300 patients with migraine, for example, 27 percent of patients who administered 2 mg of intranasal dihydroergotamine had resolution of their headache within 30 minutes [128]. By four hours after treatment, 70 percent of the headaches were resolved and returned within 24 hours in only 14 percent. No serious adverse effects of treatment were observed.

A delivery system targeting the upper nasal cavity may improve systemic availability of dihydroergotamine. In an open-label study of 360 patients with migraine, 52 percent of patients reported resolution of the most bothersome migraine symptom and 66 percent reported pain relief at two hours when using dihydroergotamine mesylate delivered to the upper nasal cavity [127]. The most common treatment-related adverse effects were nasal congestion (15 percent), nausea (7 percent), and nasal discomfort (5 percent).

Subcutaneous dihydroergotamine may be slightly more effective than the intranasal preparation, but it has the disadvantage that it does not come in a preloaded syringe. Nevertheless, patients can be taught to self-inject this agent. One study randomly assigned 295 patients with acute migraine (with or without aura) to receive 1 mg of subcutaneous dihydroergotamine or 6 mg of subcutaneous sumatriptan succinate; a second injection of the same drug was used in two hours if patients did not experience initial relief [123]. Headache relief occurred in 86 and 83 percent by four hours, respectively, a difference that was not statistically significant. However, dihydroergotamine was more likely to produce relief by 24 hours (90 versus 77 percent) and was associated with a lower incidence of recurrence in the 24 hours after therapy (18 versus 45 percent).

Dihydroergotamine should not be used within 24 hours of triptans or other ergot-like agents. Dihydroergotamine is contraindicated in patients with hypertension or ischemic heart disease, and in pregnancy. Dihydroergotamine should not be used in combination with peripheral and central vasoconstrictors or with potent inhibitors of CYP3A4 (including protease inhibitors, azole antifungals, and some macrolide antibiotics) and in patients with hemiplegic migraine or migraine with brainstem aura.

Ergotamine — It is unclear if it is the ergotamine itself or the other ingredients in the combination drugs that provide the most effect. There are two observations that question the efficacy of ergotamine alone: oral and rectal ergotamine have a very poor bioavailability (2 and 5 percent, respectively) [129], and most placebo-controlled trials of oral ergotamine alone have failed to show efficacy in the relief of migraine [130]. One controlled trial found that rectal suppositories containing ergotamine (2 mg) plus caffeine (100 mg) were as

effective as sumatriptan (25 mg) suppositories for migraine headache relief [131,132]. However, there were more side effects among patients treated with ergotamine.

Ergotamine tartrate may be associated with significant side effects and may worsen the nausea and vomiting associated with migraine. In addition, vascular occlusion and rebound headaches have been reported with oral doses exceeding 6 tablets per 24 hours or 10 tablets per week. Years of use also may be associated with valvular heart disease [133].

Ergotamine should not be used within 24 hours of triptans or other ergot-like agents. Ergots should be avoided in patients with coronary artery disease because they cause sustained coronary artery constriction [134], peripheral vascular disease, hypertension, and liver or kidney disease. In addition, ergotamine overuse has been associated with an increased risk of cerebrovascular, cardiovascular, and peripheral ischemic complications, particularly among those using cardiovascular drugs [135]. They also should not be used in patients who have hemiplegic migraine, migraine with brainstem aura, and migraine with prolonged aura because they may reduce cerebral blood flow.

A European consensus panel reviewed the use of ergotamine for the acute treatment of migraine and concluded that ergotamine is the drug of choice in relatively few patients with migraine because of issues of efficacy and side effects [131]. Suitable candidates may be those with prolonged duration of attacks (eg, greater than 48 hours) and possibly frequent headache recurrence.

ABORTIVE THERAPY PLUS PARENTERAL DEXAMETHASONE

For patients who present to the emergency department with severe or prolonged migraine, we suggest adjunctive intravenous (IV) dexamethasone along with an abortive agent to reduce the risk of early headache recurrence. However, frequent use of adjunctive dexamethasone for headache increases the risk of glucocorticoid toxicity and should be avoided.

In a meta-analysis of seven randomized trials conducted in emergency departments or headache clinics, parenteral treatment with dexamethasone was found to reduce the rate of early headache recurrence when added to standard acute migraine therapy [136]. All patients (n = 738) received standard abortive migraine headache treatment and were also randomly assigned to treatment with either a single IV or intramuscular (IM) dose of dexamethasone or placebo. In the pooled results, dexamethasone was significantly more effective than placebo for reducing migraine recurrence from 24 to 72 hours after treatment (relative risk 0.74, 95% CI 0.6-0.9). The number needed to treat to prevent one recurrent headache was nine. There were no significant differences regarding adverse events between the dexamethasone and placebo groups. However, dexamethasone provided no additional

benefit for immediate relief of headache. Similar results were found in a second meta-analysis and a systematic review [137,138].

We suggest using dexamethasone as a single IV dose of 4 mg. Initial trials reported benefit with single doses of IV dexamethasone at a range of 8 to 24 mg [136,137]. However, treatment benefits were similar whether trials used doses less than 15 mg or higher doses [136]. Subsequent trial data have found similar benefit with low dexamethasone dosing. In a 2023 trial of 209 patients with moderate to severe migraine presenting to the emergency department treated with metoclopramide and dexamethasone, the rates of sustained relief at 48 hours were similar whether patients were assigned to a single dose of dexamethasone at 4 or 16 mg (34 versus 41 percent, absolute difference 7 percent, 95% CI -6 to 20 percent) [139]. Similar results for low- and high-dose dexamethasone groups were also found in the rate of immediate headache relief as well as the subsequent number of headache days and rates of headache medication use in the week following discharge. Adverse effects in both groups were rare.

Adjunctive treatment of acute migraine with oral prednisone was not beneficial for prevention of recurrent headache in a small trial [140].

SODIUM VALPROATE

Limited data suggest that intravenous (IV) sodium valproate may be effective for acute migraine treatment. In a small trial of 99 adults with migraine without aura presenting acutely to an emergency department, patients who were given a single dose of IV sodium valproate at 800 mg were likelier to report pain relief by two hours than those who received 800 mg of ibuprofen [141]. Similar benefit was found in small studies when sodium valproate was compared with sumatriptan and dexamethasone [142,143]. However, other studies have suggested only short-term benefit with higher rates of rescue therapy with sodium valproate than antiemetics and analgesics [18,144].

Intravenous valproate is preferred over oral formulations for acute migraine treatment because it is faster acting. The typical dose is 500 to 1000 mg over 5 to 10 minutes (up to 10 mg/kg each minute). Adverse effects with valproate include nausea, vomiting, and tremor. Valproate for migraine treatment is contraindicated in pregnant patients due to an elevated risk of teratogenicity.

NEUROMODULATION

Limited data from small randomized controlled trials suggest benefit of various forms of neuromodulation for the treatment of acute migraine pain. These treatments stimulate the

central or peripheral nervous system with an electrical current or a magnetic field [145]. They are options for patients who prefer nonpharmacologic treatments or who have an inadequate response, inability to tolerate, or contraindications to drug treatments for migraine.

Transcutaneous supraorbital nerve stimulation — Transcutaneous supraorbital nerve stimulation can reduce migraine pain intensity, as shown in the ACME trial, which randomly assigned 109 subjects having an acute migraine attack of at least three hours duration to a one-hour treatment session with external trigeminal nerve stimulation or sham stimulation [146]. Pain was assessed using a visual analog scale, ranging from 0 (no pain) to 10 (maximum pain). The mean reduction in pain intensity at one hour was greater for the true stimulation group compared with the sham group (-3.46 versus -1.78). There were five minor adverse events and no serious adverse events in the true stimulation group.

The supraorbital transcutaneous trigeminal nerve stimulator device used in this trial is approved for marketing in the United States, Canada, Europe, and several additional countries. The evidence pertaining to migraine prevention is reviewed separately. (See "Preventive treatment of episodic migraine in adults", section on 'Neuromodulation'.)

Remote electrical neuromodulation — Data from several trials suggest that a device applying nonpainful electrical skin stimulation can reduce acute migraine pain [147-149]. The stimulating device, controlled with a smartphone, consists of an armband with rubber electrodes and a power source. The armband is applied, and stimulation started as soon as possible after the onset of a migraine attack. In a sham-controlled crossover pilot trial of 71 patients, the proportion of responders was higher with active stimulation compared with sham stimulation [147].

A later trial of 252 adults with episodic migraine tested randomized patients in a 1:1 ratio to receive 30 to 45 minutes of active stimulation (frequency 100 to 120 Hz, pulse width 400 microseconds, and output current up to 40 mA adjusted by the patient) or sham stimulation (pulse frequency approximately 0.08 Hz, modulated pulse width 40 to 550 microseconds) [148]. Sham stimulation was designed to produce a sensation similar to active stimulation but with a frequency too low to induce pain inhibition. At two hours after treatment, more patients assigned to active stimulation were pain-free (37 percent, versus 18 percent with sham, absolute risk difference [ARD] 19 percent) or had pain relief, defined as an improvement from severe or moderate pain to mild or none, or from mild pain to none (67 versus 39 percent, ARD 28 percent). Mild device-associated adverse events occurred in approximately 4 percent and included a warm sensation, arm or hand numbness, redness, itching, tingling, muscle spasm, arm pain, shoulder pain, and neck pain. There were no serious adverse events.

The remote electrical neuromodulation device used in this trial is approved for marketing in the United States.

Transcranial magnetic stimulation — The efficacy of single-pulse transcranial magnetic stimulation (TMS) was demonstrated in a sham-controlled trial of 201 adults with episodic migraine with aura [150]. The analysis was based upon 164 patients who treated at least one attack of migraine during the aura phase. Pain freedom at two hours post-treatment was significantly greater with the TMS device compared with sham stimulation (39 versus 22 percent, absolute risk reduction 17 percent, 95% CI 3-31 percent). Furthermore, significance for a sustained pain-free response was maintained at both 24 and 48 hours. There were no serious adverse events related to use of the device.

The portable TMS device is available in the United Kingdom and the United States. The TMS device may prove to be useful as a second-line intervention for those who have migraine that does not respond to first-line therapy with triptans or other agents discussed above or who are unable to take these agents because of contraindications or intolerance. TMS should not be used to treat migraine for patients who have epilepsy, since there is theoretical concern that TMS could trigger seizures [151].

Noninvasive vagus nerve stimulation — Noninvasive vagus nerve stimulation (nVNS) may be beneficial for the acute treatment of episodic migraine. The PRESTO trial randomly assigned over 240 participants to treatment with a proprietary nVNS device or a sham device [152]. Subjects were instructed to self-administer stimulation for 120 seconds each to right and left sides of the neck within 20 minutes from the onset of migraine pain, and to repeat stimulation, if not pain-free, at 15 minutes and 120 minutes. More patients achieved pain freedom with nVNS compared with sham, but the difference was not significant at 120 minutes (30 versus 20 percent). The most common adverse effects in the nVNS group were discomfort at the application site and nasopharyngitis. The nVNS device used in this trial is approved for marketing in the United States and European Union.

PERIPHERAL NERVE BLOCKS

Nerve blocks targeting the occipital nerve, sphenopalatine ganglion, and trigeminal nerve are options for the acute treatment of migraine in patients who have severe and prolonged migraine attacks, and in patients who are refractory to or have contraindications to standard migraine treatments [153,154]. The most important contraindications to peripheral nerve blocks include known allergy to a local anesthetic, open skull defect, and overlying skin infection; pregnancy is a relative contraindication. (See "Headache during pregnancy and postpartum".)

Evidence of efficacy is limited mainly to small, low-quality trials.

- **Occipital nerve blocks** – A sham-controlled trial enrolled patients with migraine from the emergency department who had persistent headache one hour or more after treatment with intravenous metoclopramide [155]. The primary outcome of headache freedom at 30 minutes was achieved by 4 of 13 (31 percent) treated with bilateral greater occipital nerve blocks, and none of 15 patients (0 percent) who received sham therapy. There were no differences in adverse effects between the treatment groups.

- **Sphenopalatine ganglion blocks** – Commercially available intranasal devices supposedly facilitate blockade of the sphenopalatine ganglion (SPG) by topical application and passive diffusion of local anesthetic. However, anatomic research has shown that the SPG is not as close to the nasal mucosa as previously believed, raising doubt that SPG blockade can be accomplished through intranasal application of local anesthetic [156].

  Nevertheless, limited data suggest benefit of SPG blocks for treatment of acute migraine. One early trial randomly assigned patients in a 2:1 ratio to intranasal 4 percent lidocaine or saline placebo; a 50 percent reduction in headache intensity at 15 minutes was achieved by 29 patients (55 percent) treated with lidocaine compared with 6 patients (21 percent) who received placebo [157]. A later parallel-arm, randomized pilot trial enrolled patients with chronic migraine and randomly assigned them in a 2:1 ratio to repetitive SPG blocks twice weekly for six weeks with either 0.5 percent bupivacaine or saline. With efficacy data for 38 patients, pain rating scores were lower at 15 minutes, 30 minutes, and 24 hours postprocedure for patients treated with bupivacaine compared with those treated with saline [158]. However, patients treated bupivacaine had only a marginal absolute reduction in average pain intensity (1 to 1.5 units on the numerical rating scale) compared with placebo.

OPIOIDS AND BARBITURATES

Opioids and barbiturates should not be used for the treatment of migraine, except as a last resort [159]:

- Opioids generally are not as effective as migraine-specific medications for acute migraine treatment [16,17,23]. In addition, the use of opioids is complicated by their potential for tolerance, dependence, addiction, and overdose [15,20].

- There is no high-quality evidence supporting the efficacy of barbiturates (ie, butalbital-containing compounds) for acute migraine treatment [5,20].

- The use of opioids and butalbital is associated with an increased risk for the development of chronic migraine and medication overuse headache. (See "Chronic

migraine" and "Medication overuse headache: Etiology, clinical features, and diagnosis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Migraine and other primary headache disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Migraines in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Migraines in adults (Beyond the Basics)" and "Patient education: Headache treatment in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Approach to treatment** – Abortive treatments are usually more effective if they are given early in the course of the migraine attack; a large single dose tends to work better than repetitive small doses. For patients who present with significant nausea or vomiting, a nonoral (eg, intravenous [IV], intramuscular [IM], or subcutaneous) agent may be preferred. Adjunctive preventive medications may be warranted when headaches are frequent or unresponsive to acute therapies to reduce the risk of medication overuse headache. (See 'Approach to treatment' above.)

The selection of a specific agent depends on patient-specific factors including the severity and character of symptoms, comorbid conditions, and prior response to treatment (algorithm 1).

- **Patients with mild migraine attacks** – For patients with mild migraine attacks without vomiting or severe nausea, we suggest initial treatment with nonopioid analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen (table 1), rather than migraine-specific agents (**Grade 2C**). (See 'Mild attacks' above and 'Simple analgesics' above.)

  For patients unresponsive to nonopioid analgesics, we add a triptan (table 2). The combined use of an NSAID with a triptan is more effective than either agent alone. (See 'Triptans with NSAIDs' above and 'Antiemetics' above and 'Simple analgesics' above.)

- **Patients with moderate to severe migraine attacks** – For patients with moderate to severe migraine attacks, we suggest treatment with a triptan with or without a nonopioid analgesic (eg, naproxen sodium) (table 1), rather than other migraine-specific agents (**Grade 2C**). Several triptans are available in a variety of formulations (table 2). All the triptans are effective for the acute treatment of migraine and the combined use of a triptan and a nonopioid analgesic appears to be more effective than using either class alone. (See 'Moderate to severe attacks' above and 'Triptans' above and 'Triptans with NSAIDs' above.)

  When attacks are associated with severe nausea or vomiting, we add an antiemetic and/or switch to a nonoral migraine-specific medication.

  Alternative options include calcitonin gene-related peptide (CGRP) antagonists, lasmiditan, an antiemetic drug, and dihydroergotamine. (See 'CGRP antagonists' above and 'Lasmiditan' above and 'Antiemetics' above and 'Ergots' above.)

- **Patients with severe migraine attacks in an emergency department** – For patients with refractory migraine attacks who present to the hospital emergency department (ED), we suggest combination treatment that includes (**Grade 2C**) (see 'Emergency settings' above):

  - Subcutaneous sumatriptan 6 mg and/or a parenteral antiemetic agent. (See 'Triptans' above and 'Antiemetics' above.)
  - Adjunctive diphenhydramine 25 mg, if IV metoclopramide or prochlorperazine are used, to prevent akathisia and other dystonic reactions. (See 'Antiemetics' above.)
  - Adjunctive dexamethasone 4 mg (IV or IM) to reduce the risk of early headache recurrence. (See 'Abortive therapy plus parenteral dexamethasone' above.)

Alternative options include IV dihydroergotamine (DHE 45) combined with IV metoclopramide (for patients who have not receive a triptan within 24 hours), IV sodium valproate, or IM/IV ketorolac. (See 'Dihydroergotamine' above and 'Sodium valproate' above and 'Simple analgesics' above.)

- **Status migrainosus** – For patients with status migrainosus (ie, a debilitating attack lasting for more than 72 hours), we suggest a combination of intravenous fluids plus parenteral medications, including ketorolac and a dopamine receptor blocker (eg, prochlorperazine, metoclopramide, chlorpromazine) (**Grade 2C**). Other options include valproate and/or dihydroergotamine; some patients may require admission for persistent disabling symptoms. (See 'Status migrainosus' above.)

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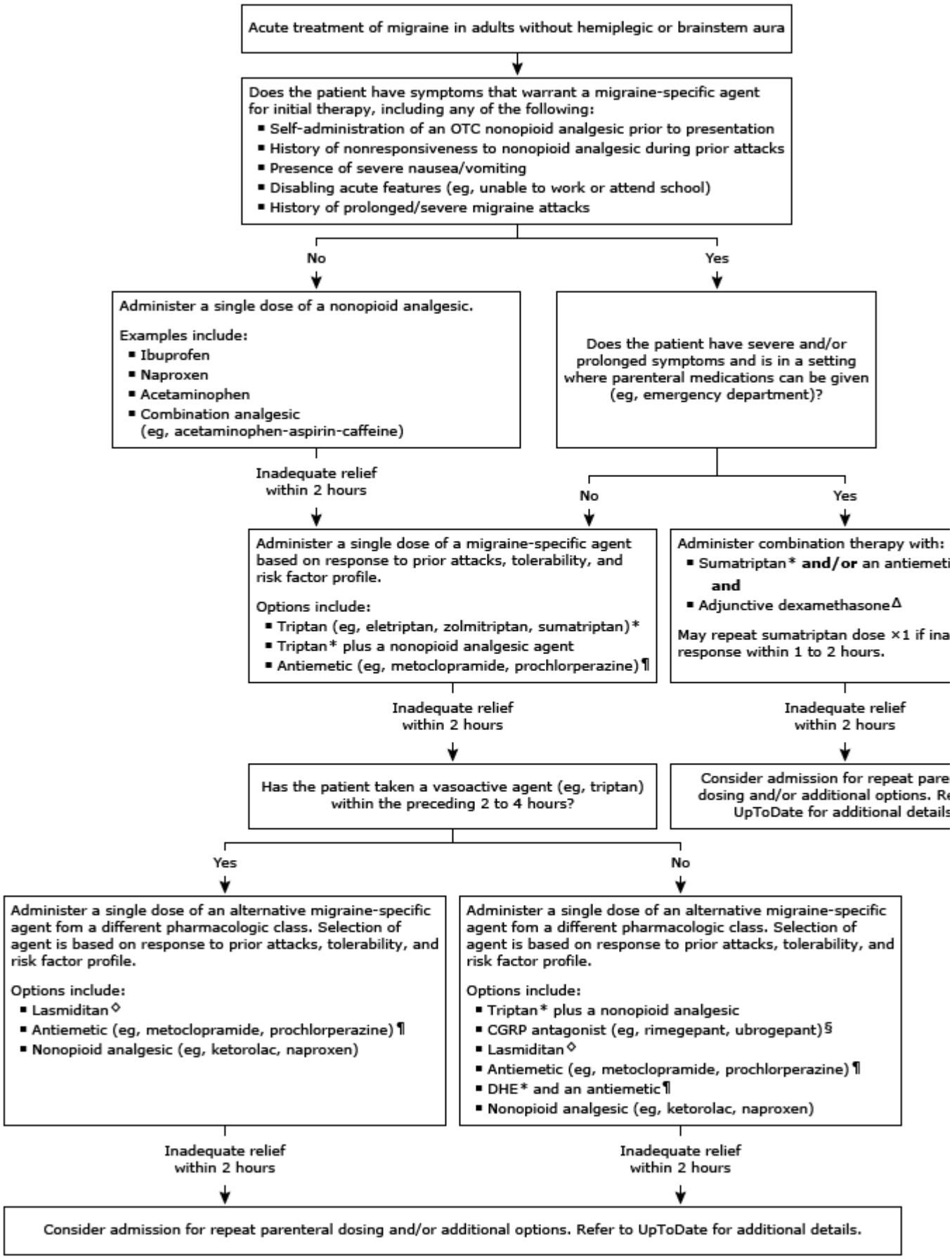
Topic 3347 Version 102.0

GRAPHICS

Acute treatment of migraine in adults without hemiplegic or brainstem aura



Pharmacologic treatment of nonpregnant adults with acute migraine should be given early following symptom onset to maximize efficacy and reduce the risk of adverse effects and medication overuse headache. The selection of a specific agent depends on patient-specific factors including the severity and character of symptoms, comorbid conditions, and prior response to treatment. Repeat dosing may be required for patients who report inadequate relief with initial therapy. Parenteral options with or without an antiemetic agent may be preferred for faster onset of efficacy and for patients with severe nausea/vomiting who are unable to tolerate oral options. Adjunctive prophylactic treatment may be started for patients with headaches that are frequent, long-lasting, and/or disabling. Refer to UpToDate topics for additional details.

OTC: over the counter (nonprescription); triptan: serotonin 1b/1d agonist; CGRP: calcitonin gene-related peptide; DHE: dihydroergotamine.

* Triptans and DHE should be avoided in patients with hemiplegic migraine or migraine with brainstem aura and those with a history of ischemic stroke, vaso-occlusive arterial disease, and uncontrolled hypertension. Initial dose for most triptan formulations may be repeated in two hours; refer to Lexicomp drug monographs for product-specific details. Triptans or DHE should not be started within 24 hours of the use of an alternative ergotamine or a different triptan agent.

¶ Dopamine receptor blocking antiemetic agents are typically used along with diphenhydramine to prevent akathisia and acute dystonic reactions. In addition, oral or intravenous fluids should also be administered to patients with suspected volume depletion due to reduced oral intake and/or recurrent vomiting. Dopamine blockers can lead to cardiac arrhythmias and should be avoided in patients with congenital or acquired long QT syndrome.

Δ Adjunctive dexamethasone is given to reduce the frequency of early migraine recurrence, but use should be limited to patients with refractory migraine, status migrainosus, and those with a history of frequent recurrent migraine attacks to reduce the risk of adverse effects. Refer to UpToDate for additional details.

◇ Lasmiditan may cause dizziness and/or somnolence; patients should not drive a motor vehicle or otherwise engage in potentially hazardous activities for at least eight hours after use of lasmiditan.

§ Initial dose of ubrogepant may be repeated in two hours. The safety of CGRP antagonists within two to four hours of a triptan or DHE is not well established.

Graphic 142189 Version 2.0

Nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (paracetamol): Usual oral dosing for adults with pain or inflammation and selected characteristics

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Nonselective NSAIDs*			
Acetic acids			
Diclofenac¶	50 mg every 8 to 12 hours	150 mg For rheumatoid arthritis, labeling in United States permits up to 200 mg Approved maximum in Canada is 100 mg	▪ Dosing for free-acid preparation differs from doses listed here for sodium or potassium salts; refer to Lexicomp drug monograph
Etodolac	200 to 400 mg every 6 to 8 hours	1000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at lower total daily dose of 600 to 800 mg
Indomethacin	25 to 50 mg every 8 to 12 hours	150 mg For rheumatologic conditions, labeling in United States permits up to 200 mg	▪ Used for treatment of acute gout and certain types of headache ▪ Potent inhibitory effects on kidne prostaglandin synthesis ▪ More frequently associated with CNS side effects (eg, headache, altered mental status) compared with other NSAIDs
Sulindac	150 to 200 mg every 12 hours	400 mg	▪ Rarely used ▪ More frequently associated with hepatic inflammation than other NSAIDs ▪ Metabolites implicated in the formation of renal calculi
Fenamates			
Meclofenamate (meclofenamic acid)	50 mg every 4 to 6 hours or	400 mg	▪ Used for treatment of dysmenorrhea ▪ Relatively higher incidence of GI side effects

	100 mg 3 times daily up to 6 days for dysmenorrhea		
Mefenamic acid	250 mg every 6 hours or 500 mg 3 times daily	1000 mg For dysmenorrhea, up to 1500 mg	▪ Used for treatment of dysmenorrhea; not indicated for treatment of chronic pain or inflammation ▪ Do not exceed 3 days (dysmenorrhea) to 7 days (acute pain) of use ▪ Less potent antiinflammatory effect
Nonacidic			
Nabumetone	1000 mg once to twice daily	2000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at daily dose ≤1000 mg
Oxicams			
Meloxicam[Δ]	7.5 to 15 mg once daily (conventional tablet, oral suspension) 5 to 10 mg once daily (capsule)	15 mg (conventional tablet, oral suspension) 10 mg (capsule)	▪ Long duration of effect; relatively slow onset ▪ Relative COX-2 selectivity and minimal effect on platelet function at lower daily dose of 7.5 mg
Piroxicam	10 to 20 mg once daily	20 mg	▪ Long-acting alternative for treatment of chronic pain and inflammation poorly responsive to other NSAIDs ▪ Prescribing generally limited to specialists with experience in treatment of chronic pain and inflammation
Propionic acids			
Fenoprofen	200 mg every 4 to 6 hours or 400 to 600 mg every 6 to 8 hours	3200 mg	▪ More frequently associated with acute interstitial nephritis and nephrotic syndrome[1]
Flurbiprofen	50 mg every 6 hours or 100 mg every 8 to 12 hours	300 mg	

Ibuprofen[Δ]	400 mg every 4 to 6 hours or 600 to 800 mg every 6 to 8 hours	3200 mg (acute), 2400 mg (chronic)	▪ Shorter-acting alternative to naproxen; useful in patients without cardiovascular risks
Ketoprofen	50 mg every 6 hours or 75 mg every 8 hours	300 mg	
Naproxen	Base: 250 to 500 mg every 12 hours or 250 mg every 6 to 8 hours Naproxen sodium: 275 to 550 mg every 12 hours or 275 mg every 6 to 8 hours	Base: 1250 mg (acute); 1000 mg (chronic); may increase to 1500 mg during a disease flare Naproxen sodium: 1375 mg (acute); 1100 mg (chronic); may increase to 1650 mg during a disease flare	▪ Often preferred by UpToDate for treatment of acute or chronic pai and inflammation in patients without relevant comorbidities or risks ▪ Higher dose (eg, 500 mg base twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs;[2] refer to UpToDate topic review of cardiovascular effects of nonselective NSAIDs ▪ Naproxen sodium has a faster onset than naproxen base
Oxaprozin	1200 mg once daily	1200 mg or 1800 mg depending on body weight (refer to Lexicomp drug monograph)	▪ Prolonged half-life (41 to 55 hours); requires several days of treatment to reach full effect
Salicylate (acetylated)			
Aspirin	325 to 1000 mg every 4 to 6 hours	4000 mg	▪ Not commonly used for chronic pain and inflammation ▪ High daily doses have been used as antiinflammatory therapy; such use is limited by toxicity ▪ Irreversibly inhibits platelet function ▪ Refer to appropriate UpToDate clinical topics and Lexicomp drug monograph for other uses
Salicylates (nonacetylated)			
Diflunisal	500 mg every 8 to 12 hours	1500 mg	▪ No significant effect on platelet function at usual doses ▪ Relatively lower GI bleeding risk than other nonselective NSAIDs a usual doses
Magnesium salicylate	1160 mg every 6 hours	4640 mg	

			▪ May be tolerated at lower daily doses by adults with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis); refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Salsalate	1000 mg every 8 to 12 hours or 1500 mg every 12 hours	3000 mg	
COX-2 selective NSAIDs			
Celecoxib	200 mg daily or 100 mg every 12 hours	400 mg	▪ Less risk of GI toxicity relative to nonselective NSAIDs; benefit negated by low-dose aspirin, which may require concurrent gastroprotection ▪ No effect on platelet function ▪ Cardiovascular and kidney risks are dose-related and may be similar to nonselective NSAIDs ▪ May be tolerated by patients with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis) who cannot take other NSAIDs; refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Etoricoxib (not available in the United States)	30 to 60 mg once daily	60 mg (chronic pain and inflammation) 120 mg (acute pain for up to 8 days)	▪ May be associated with more frequent and severe dose-related cardiovascular effects (eg, hypertension) ▪ Other risks and benefits similar to celecoxib
Non-NSAID analgesic			
Acetaminophen (paracetamol)[Δ]	325 to 650 mg every 4 to 6 hours or 1000 mg every 6 hours up to 3 times daily	3000 mg 4000 mg in selected medically supervised patients Avoid or use a lower total daily dose (maximum 2000 mg) in older adults, patients at increased risk for hepatotoxicity (eg, regular	▪ Effective for noninflammatory pain; may decrease opioid requirements ▪ Doses ≤2000 mg per day do not appear to increase risk of serious GI complications[3] ▪ Does not alter platelet function ▪ Can cause hepatotoxicity in chronic or acute overdose ▪ To avoid overdose, warn patients about acetaminophen content in combination prescription (eg, oxycodone-acetaminophen) and

		alcohol use, malnourished), or patients with organ dysfunction	nonprescription (OTC) preparations

NSAIDs are useful for treatment of acute and chronic painful and inflammatory conditions and may reduce opioid requirements. The indications for use of NSAIDs in specific disorders, adverse effects, and toxicities are presented in the relevant UpToDate topics including reviews of NSAID-associated adverse cardiovascular effects, gastroduodenal toxicity, acute kidney injury, etc.

UpToDate contributors generally avoid use of NSAIDs, or use them with particular caution and at reduced doses, in older adults and patients (regardless of age) with existing or increased risk for cardiovascular, GI, or kidney disease. Concurrent gastroprotection (eg, a proton pump inhibitor) may be warranted. For information on gastroprotective strategies, including use of selective COX-2 inhibitors and other options, refer to the UpToDate topic reviews of COX-2 selective NSAIDs and NSAIDs (including aspirin) and primary prevention of gastroduodenal toxicity.

Short- to moderate-acting NSAIDs (eg, naproxen, ibuprofen) are preferred for most patients. Use the lowest effective dose for the shortest duration of time. For chronic inflammatory conditions, a trial of ≥2 weeks is advised to assess full efficacy. For patients who experience an inadequate response to an NSAID of 1 class, it is reasonable to substitute an NSAID of another class.

Dosing in this table is for immediate-release preparations in patients with normal organ (eg, kidney) function. For treatment of acute pain, a loading dose of some NSAIDs may be used; refer to Lexicomp drug monographs.

Drug interactions may be determined by use of the Lexicomp drug interactions program included within UpToDate.

AERD: aspirin-exacerbated respiratory disease; CNS: central nervous system; COX-2: cyclooxygenase, isoform 2; GI: gastrointestinal; OTC: over the counter.

* Nonselective NSAIDs reversibly inhibit platelet function, with some exceptions noted above.

¶ Also available as a topical agent.

Δ Also available for parenteral use.

References:

1. *Murray MD, Brater DC. Renal toxicity of the nonsteroidal anti-inflammatory drugs. Annu Rev Pharmacol Toxicol 1993; 33:435.*
2. *Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. Lancet 2013; 382:769.*
3. *McCrae JC, Morrison EE, MacIntyer IM, et al. Long-term adverse effects of paracetamol – a review. Br J Clin Pharmacol 2018; 84:2218.*

Graphic 70067 Version 71.0

Triptans (serotonin 1b/1d agonists) for acute treatment of adults with migraine

Triptan	Route (preparations)	Typical initial dose	Maximum dose per 24 hours	Notes
Sumatriptan	Oral (tablet)	50 to 100 mg	200 mg	
	SUBQ (solution for injection)	6 mg	12 mg	▪ More efficacious than oral route with greater adverse effects ▪ May repeat dose after 1 hour ▪ If 6 mg dose is not tolerated, may use reduced dose (eg, 3 or 4 mg) ▪ Autoinjectors (3 mg, 4 mg or 6 mg) are also available
	Intranasal (spray and powder)			▪ DDM additive increases rate of absorption; nasal spray coformulated with DDM is used at a lower dose (ie, 10 mg), which may be repeated after 1 hour
	Spray (Imitrex and generics)	20 mg in one nostril	40 mg	
	Spray (coformulated with DDM; Tosymra)	10 mg in one nostril	30 mg	
	Powder	22 mg (11 mg capsule insufflated in each nostril)	44 mg	
Zolmitriptan	Oral (tablet and ODT)	2.5 to 5 mg	10 mg	▪ Oral tablet (but not ODT) may be split to achieve smaller dose
	Intranasal (solution)	2.5 or 5 mg in one nostril	10 mg	▪ Less taste disturbance than intranasal sumatriptan
Eletriptan	Oral (tablet)	20 to 40 mg	80 mg	▪ In general, 40 mg dose is recommended due to greater efficacy, however 20 mg may be better tolerated ▪ Metabolized by CYP3A4; do not use within 72 hour

				of a CYP3A4 inhibitor*
Rizatriptan	Oral (tablet, ODT, film)	Tablet, ODT: 5 to 10 mg Film: 10 mg	30 mg	▪ Use reduced dose in patients taking propranolol* ▪ Do not split 10 mg film to achieve a smaller dose
Almotriptan	Oral (tablet)	12.5 mg	25 mg	▪ May be better tolerated than many other triptans ▪ Metabolized by CYP3A4; dose adjustment or avoidance may be required with CYP3A4 inhibitors*
Naratriptan	Oral (tablet)	2.5 mg	5 mg	▪ Slower onset and longer duration of effect than many other triptans ▪ May have lower efficacy but be better tolerated than many other triptans ▪ May repeat dose after 4 hours
Frovatriptan	Oral (tablet)	2.5 mg	5 mg	▪ Slower onset and longer duration of effect than many other triptans ▪ May have lower efficacy but be better tolerated than many other triptans

Several triptans are effective options for acute treatment of migraine. Choice of triptan should be individualized; patients who do not respond well to one triptan may respond to another. For patients using a triptan, treatment should be started early after onset of migraine symptoms. Dose may be repeated after two hours if response to initial dose is suboptimal, unless otherwise noted, up to the maximum dose in a 24-hour period. Triptans should not be administered within 24-hour use of another triptan or ergotamine agents. Limit use to less than 10 days per month to avoid medication-overuse headache. Triptans should be avoided for patients with hemiplegic migraine or migraine with brainstem aura and those with a history of ischemic stroke, ischemic heart disease, uncontrolled hypertension, and pregnancy. Refer to UpToDate for additional details.

CYP3A4: cytochrome P450 isoenzyme 3A4; DDM: n-Dodecyl beta-D-maltoside; ODT: orally disintegrating tablet; SUBQ: subcutaneous.

* Refer to the drug interactions program for specific recommendations.

Graphic 141582 Version 5.0

Some reported causes and potentiators of the long QT syndrome

Congenital

- Jervell and Lange-Nielsen syndrome (including "channelopathies")
- Romano-Ward syndrome
- Idiopathic

Acquired

Metabolic disorders

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Starvation
- Anorexia nervosa
- Liquid protein diets
- Hypothyroidism

Bradyarrhythmias

- Sinus node dysfunction
- AV block: Second or third degree

Other factors

- Myocardial ischemia or infarction, especially with prominent T-wave inversions
- Intracranial disease
- HIV infection
- Hypothermia
- Toxic exposure: Organophosphate insecticides

Androgen deprivation therapy

- GnRH agonist/antagonist therapy
- Bilateral surgical orchiectomy

Diuretic therapy via electrolyte disorders particularly hypokalemia and hypomagnesemia

Herbs

- Cinchona (contains quinine), iboga (ibogaine), licorice extract in overuse via electrolyte disturbances

Medications*

High risk

- Adagrasib
- Ajmaline¶
- Amiodarone△
- Arsenic trioxide
- Astemizole◇
- Bedaquline
- Bepridil◇
- Chlorpromazine
- Cisaparide (restricted availability)
- Delamanid¶
- Disopyramide△
- Dofetilide
- Dronedarone
- Haloperidol (IV)
- Ibutilide
- Ivosidenib
- Lenvatinib
- Levoketoconazole
- Methadone
- Mobocertinib
- Papavirine (intracoronary)
- Procainamide
- Quinidine
- Quinine
- Selpercatinib
- Sertindole¶
- Sotalol
- Terfenadine◇
- Vandetanib
- Vernakalant¶
- Ziprasidone

Moderate risk

- Amisulpride¶ (oral)§
- Azithromycin
- Capecitabine
- Carbetocin¶
- Certinib
- Chloroquine
- Citalopram
- Encorafenib
- Entrectinib
- Erythromycin
- Escitalopram
- Etelcalcetide
- Fexinidazole
- Flecainide
- Levetiracetam
- Levofloxacin (systemic)
- Lofexidine
- Meglumine antimoniate
- Midostaurin
- Quetiapine
- Quizartinib
- Ribociclib
- Risperidone
- Saquinavir
- Sevoflurane
- Sparfloxacin¶

- Clarithromycin
- Clofazimine
- Clomipramine[¥]
- Clozapine
- Crizotinib
- Dabrafenib
- Dasatinib
- Deslurane
- Domperidone[¶]
- Doxepin[¥]
- Doxifluridine[¶]
- Droperidol
- Floxuridine
- Fluconazole
- Fluorouracil (systemic)
- Flupentixol[¶]
- Gabobenate dimeglumine
- Gemifloxacin[¶]
- Gilteritinib
- Halofantrine
- Haloperidol (oral)
- Imipramine[¥]
- Inotuzumab ozogamacin
- Isoflurane
- Moxifloxacin
- Nilotinib
- Olanzapine
- Ondansetron (IV > oral)
- Osimertinib
- Oxytocin
- Pazopanib
- Pentamidine
- Pilsicainide[◇]
- Pimozide
- Piperaquine
- Probucol[◇]
- Propafenone
- Propofol
- Sunitinib
- Tegafur[¶]
- Terbutaline
- Thioridazine
- Toremifene
- Vemurafenib
- Voriconazole

Low risk[‡]

- Albuterol
- Alfuzosin
- Amisulpride (IV)[§]
- Amitriptyline[¥]
- Anagrelide
- Apomorphine
- Arformoterol
- Artemether-lumefantrine
- Asenapine
- Atomoxetine
- Benperidol
- Bilastine[¶]
- Bosutinib
- Bromperidol
- Buprenorphine[†]
- Buserelin
- Ciprofloxacin (Systemic)
- Cocaine (Topical)
- Degarelix
- Desipramine[¥]
- Deutetrabenazine
- Dexmedetomidine[**]
- Dolasetron
- Donepezil
- Efavirenz
- Fingolimod
- Fluoxetine
- Fluphenazine
- Fluvoxamine
- Formoterol
- Foscarnet
- Fostemsavir
- Gadofosveset
- Gepirone
- Glasdegib
- Goserelin
- Granisetron
- Hydroxychloroquine (rare reports)
- Hydroxyzine
- Iloperidone
- Indacaterol
- Itraconazole
- Ketoconazole (systemic)
- Lacidipine
- Lapatinib
- Lefamulin
- Leuprolide
- Leuprolide-norethindrone
- Levalbuterol
- Macimorelin
- Maprotiline
- Mefloquine
- Mequitazine
- Metoclopramide (rare reports)
- Metronidazole (systemic)
- Mifepristone
- Mirtazapine
- Mizolastine
- Nelfinavir
- Norfloxacin
- Nortriptyline[¥]
- Ofloxacin (systemic)
- Olodaterol
- Osilodrostat
- Oxaliplatin
- Ozanimod[ΔΔ]
- Pacritinib
- Paliperidone
- Panobinostat
- Paroxetine
- Pasireotide
- Pefloxacin
- Periciazine[¶]
- Pimavanserin
- Promazine
- Radotinib
- Ranolazine (due to bradycardia)
- Relugolix
- Rilpivirine
- Romidepsin
- Roxithromycin
- Salmeterol
- Sertraline
- Siponimod
- Solifenacin
- Sorafenib
- Sulpiride
- Tacrolimus (systemic)
- Tamoxifen
- Telavancin
- Teneligliptin
- Tetrabenazine
- Trazodone
- Triclabendazole
- Triptorelin
- Tropisetron[¶]
- Vardenafil
- Vilanterol
- Vinflunine

▪ Eliglustat ▪ Eribulin ▪ Etrasimod ▪ Ezogabine	▪ Levomepromazine (methotrimeprazine) ▪ Levomethadone ▪ Lithium ▪ Loperamide¶¶ in overdose ▪ Lopinavir	▪ Pipamperone ▪ Pitolisant ▪ Ponesimod ▪ Primaquine	▪ Voclosporin ▪ Vorinostat ▪ Zuclopenthixol

This is not a complete list of all corrected QT interval (QTc)-prolonging drugs and does not include drugs with either a minor degree or isolated association(s) with QTc prolongation that appear to be safe in most patients but may need to be avoided in patients with congenital long QT syndrome depending upon clinical circumstances. A more complete list of such drugs is available at the CredibleMeds website. For clinical use and precautions related to medications and drug interactions, refer to the UpToDate topic review of acquired long QT syndrome discussion of medications and the drug interactions program.

AV: atrioventricular; IV: intravenous; QTc: rate-corrected QT interval on the electrocardiogram.

* Classifications provided by Lexicomp according to US Food & Drug Administration guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017 (revision 2) available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf as updated August 8, 2023 (https://www.fda.gov/media/170814/download) with additional data from CredibleMeds QT drugs list[1,2]. The use of other classification criteria may lead to some agents being classified differently by other sources.

¶ Not available in the United States.

Δ In contrast with other class III antiarrhythmic drugs, amiodarone is rarely associated with torsades de pointes; refer to accompanying text within UpToDate topic reviews of acquired long QT syndrome.

◇ Withdrawn from market in most countries due to adverse cardiovascular effects.

§ IV amisulpride antiemetic use is associated with less QTc prolongation than the higher doses administered orally as an antipsychotic.

¥ Some other cyclic antidepressants (ie, amoxapine, protriptyline, trimipramine) may also prolong the QT interval, but data are insufficient to identify level of risk with confidence; refer to UpToDate content on cyclic antidepressant pharmacology, administration, and side effects.

‡ The "low risk" category includes drugs with limited evidence of clinically significant QTc prolongation or TdP risk; many of these drugs have label warnings regarding possible QTc effects or recommendations to avoid use or increase ECG monitoring when combined with other QTc prolonging drugs.

† Rarely associated with significant QTc prolongation at usual doses for treatment of opioid use disorder, making buprenorphine a suitable alternative for patients with methadone-associated QTc prolongation. Refer to UpToDate clinical topic reviews.

** The United States FDA labeling for the sublingual preparation of dexmedetomidine warns against use in patients at elevated risk for QTc prolongation. Both intravenous (ie, sedative) and sublingual formulations of dexmedetomidine have a low risk of QTc prolongation and have **not** been implicated in TdP.

¶¶ Over-the-counter; available without a prescription.

ΔΔ Not associated with significant QTc prolongation in healthy persons. Refer to UpToDate clinical topic for potential adverse cardiovascular (CV) effects in patients with CV disease.

Data from:

1. *Lexicomp Online. Copyright ©1978-2024 Lexicomp, Inc. All Rights Reserved.*
2. *CredibleMeds QT drugs list website sponsored by Science Foundation of the University of Arizona. Available at http://crediblemeds.org/.*

Graphic 57431 Version 151.0

Contributor Disclosures

Todd J Schwedt, MD, MSCI Equity Ownership/Stock Options: Aural Analytics [Neurology]; Nocira [Headache]. Grant/Research/Clinical Trial Support: Amgen [Migraine/Headache]. Consultant/Advisory Boards: AbbVie [Migraine/Headache]; Allergan [Migraine/Headache]; Amgen [Migraine/Headache]; Axsome [Migraine/Headache]; Biodelivery Science [Migraine/Headache]; Biohaven [Migraine/Headache]; Click Therapeutics [Migraine/Headache]; Collegium [Migraine/Headache]; Eli Lilly [Migraine/Headache]; Ipsen [Migraine/Headache]; Linpharma [Migraine/Headache]; Lundbeck [Migraine/Headache]; Novartis [Migraine/Headache]; Satsuma [Migraine/Headache]; Tonix Pharma [Migraine/Headache]. All of the relevant financial relationships listed have been mitigated. **Ivan Garza, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Jerry W Swanson, MD, MHPE** Other Financial Interest: Elsevier [Honorarium as editor of texts about migraine]. All of the relevant financial relationships listed have been mitigated. **Richard P Goddeau, Jr, DO, FAHA** No relevant financial relationship(s) with ineligible companies to disclose.

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