بسم الله الرحمن الرحیم

In The Name of God

Acute treatment of migraine

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Introduction

- Migraine affects approximately 15% of the population.
- The likelihood for migraine is highest between 25 and 55 years of age, the prime working years.
- It is the second leading cause of time lost to disability, after low back pain
- More than one-half of the workdays lost to headache are a result of migraine.
- The personal burden of migraine weighs not only on people with migraine, but also on family and friends.
- Untreated attacks or attacks that do not respond well to therapy can lead to longer attacks with greater disability and, over time, become a risk factor for patients to develop chronic migraine.

Introduction

- Significant expansion in the understanding of migraine pathophysiology has occurred over the last 20+ years.
- Knowledge of central and peripheral neural pathways, neuropeptides, and neurotransmitters has led to innovation in the treatment of migraine after decades of little change.
- The acute treatment landscape for migraine has recently expanded beyond the standard NSAIDs, analgesics, triptans, ergotamines, and combination therapies, to include neuromodulation devices, and recently approved CGRP antagonists and a serotonin (5-HT1F) receptor agonist.
- Categories of medications currently approved for acute treatment of migraine include triptans, ergotamines, NSAIDs, ditans, gepants, analgesics, and combination therapies
- Neuromodulation devices have also been approved for acute treatment of migraine.

Goals of acute treatment

- Stop the pain
- Alleviate associated symptoms of the migraine attack
- Prevent recurrence of symptoms
- Return the patient to normal function
- Plan for future attacks

Drug selection

Severity of attacks

Rapidity of symptom onset

Duration of attack

Type of migraine

Patient-specific factors

Treatment setting:

In/out patient

Previous treatments experience

Cost of medications

Drug's efficacy and safety

Acute migraine medications

- Medication for an acute attack can be specific or non- specific.
- Non- specific agents are NSAIDs, combined analgesics, antiemetics, opioids, and corticosteroids.
- Non- specific agents are indicated for mild or moderate attacks.
- Specific agents are used for the treatment of moderate- to- severe migraine and in patients whose mild- to- moderate migraine responds poorly to NSAIDS or combined analgesics.
- When choosing medication, it is also very important to select an adequate formulation and route of administration, based on severity of the attack, need for rapid relief, or the presence or absence of nausea or vomiting.

Early attack treatment

- Treating the attack when the pain is mild improves treatment efficacy.
- Early intervention can improve treatment outcomes and prevent central sensitization and attack progression. It can also increase patient satisfaction.
- Early treatment approach may not be suitable for all migraine sufferers, as attacks are highly variable and tension- type headache commonly co- occurs.
- It can also induce frequent intake of medications and increase the risk of medication overuse.
- It is important to limit the acute headache treatment to 2 days per week and use preventive treatment in patients taking acute agents for 1 or more days per week.

American and Canadian Headache Societies Guidelines for Acute Migraine Treatment

Medication	American Headache Society[8]	Canadian Headache Society[7]
Acetaminophen 1000 mg for nonincapacitating attacks	Strong evidence (Level A)	Strong evidence
Aspirin 500 mg, diclofenac 50 mg or 100 mg, ibuprofen 200 mg or 400 mg, naproxen 500 mg or 550 mg	Strong evidence (Level A)	Strong evidence
Triptans	Strong evidence (Level A)	Strong evidence
Dihydroergotamine nasal spray	Strong evidence (Level A)	Weak evidence but may be first line in some cases
Dihydroergotamine IV/IM/subcutaneous	Medium evidence (Level B)	Weak evidence but may be first line in some cases
Acetaminophen/aspirin/caffeine	Strong evidence (Level A)	Not addressed
Butorphanol nasal spray	Strong evidence (Level A)	Weak evidence, should not use
Codeine	Medium to weak evidence (Level B/C)	Weak evidence, should not use
Tramadol	Medium evidence (Level B)	Weak evidence, should not use

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.
- 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.

Nonsteroidal anti-inflammatory drugs

- There are no studies comparing the relative efficacy of different NSAIDs. If one NSAID is ineffective, a different drug may be tried.
- NSAIDs with reported efficacy in randomized placebo-controlled trials:

Ibuprofen
400-600 mg

Indomethacin
50-100 mg

Naproxen
275-825 mg

aspirin
900-1000 mg

ketorolac
30 mg IV or 60 mg IM

dexketoprofen
50mg

Diclofenac
50-100 mg

Celecoxib
200 mg

tolfenamic acid
200 mg

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.
- 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 non-oral migraine-specific medications including subcutaneous sumatriptan, nasal sumatriptan and zolmitriptan, parenteral dihydroergotamine ,or nasal zavegepant.

Status migrainosus

- These 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 may also be warranted depending on response to initial therapy.
- Administration of parenteral dexamethasone is often used to prevent attack relapse.
- Opioids should not be used in the acute treatment of migraine. Patients treated with opioids as first-line therapy are significantly more likely to return to the emergency department with a headache within seven days.
- Patients may require admission for persistent disabling symptoms despite the initial treatment regimen or for weaning of medication overuse to monitor for withdrawal symptoms.

- Reasonable options, with evidence of efficacy from randomized trials in emergency settings:

1. Sumatriptan 6 mg subcutaneous injection
2. 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)
3. Antiemetics-dopamine receptor blockers:
   - ✓Prochlorperazine 10 mg IV or IM
   - ✓Metoclopramide 10 mg IV
   - ✓Chlorpromazine 0.1 mg/kg (or 12.5 mg) single dose as a slow IV infusion (max rate 1 mg/minute); max cumulative dose 25 mg
   - ✓Adjunct use of diphenhydramine (12.5 to 25mg IV every hour up to two doses) to prevent akathisia and other dystonic reactions.
4. DHE (1 mg IV) combined with metoclopramide (10 mg IV)
5. Dexamethasone (10 to 24 mg IV or IM) to reduce the risk of early headache recurrence.

Acute attacks in pregnancy

- First-line therapy:
  - Acetaminophen(1000 mg orally)
  - Acetaminophen 650 to 1000 mg and metoclopramide 10 mg
  - Acetaminophen-codeine
- Caffeine doses in medications for migraine range from 40 to 60 mg; daily caffeine intake less than 200 mg from all sources is unlikely to be associated with adverse pregnancy effects.

Acute attacks in pregnancy

- Second-line therapy:
  - Aspirin or NSAIDs
  - Naproxen, ibuprofen, diclofenac, and ketorolac, are safest in the second trimester before 20 weeks.
  - In the 1st trimester, a possible modest increase in early pregnancy loss and some congenital anomalies has been suggested, but available evidence is limited and weak.
  - From 20 to 30 weeks, fetal renal effects leading to oligohydramnios are a concern, generally after days to weeks of treatment; treatment <48 hours is generally safe.
  - After 30 weeks, use should be avoided or limited to < 48 hours due to concerns about prenatal constriction of the ductus arteriosus, persistent pulmonary hypertension of the newborn, oligohydramnios and its sequelae, necrotizing enterocolitis, renal dysfunction or failure, and intracranial hemorrhage.

Acute attacks in pregnancy

- Third-line therapies:
  - Triptans: frovatriptan and naratriptan are less desirable than other triptans because of their longer half-life, and naratriptan is the least effective triptan.
  - Drugs to reduce nausea and vomiting
  - Opioids:
    - use should be limited to the lowest effective dose and for the shortest time required to control acute pain.
    - They may worsen the nausea/vomiting and constipation associated with pregnancy. All opioids have potential for maternal addiction and neonatal withdrawal.
  - Magnesium sulfate: 1 or 2 g intravenously over 10 to 15 minutes
  - Glucocorticoids: Prednisone (20 mg orally four times daily for two days) or methylprednisolone (4 mg orally, 21 tablets over six days)
  - Peripheral nerve block

Acute attacks in pregnancy

- Drugs to reduce nausea and vomiting:
  - Meclizine (25 mg orally), diphenhydramine (25 to 50 mg orally or 10 to 50 mg IV), and promethazine (12.5 to 25 mg orally, per rectum, or IM) are preferred in pregnancy.
  - Dopamine antagonists: metoclopramide (10 mg IV, IM, or orally) or phenothiazines such as prochlorperazine (10 mg IV, IM, or orally) or chlorpromazine (25 to 50 mg IM) are effective, but maternal acute dystonic reactions sometimes occur.
  - Ondansetron (4 to 8 mg orally or intravenously)

Avoidance of medication overuse

- The risk for MOH appears to be highest with opioids, butalbital-containing combination analgesics, and aspirin-acetaminophen-caffeine combinations.
- 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.
- MOH may be avoided with some CGRP antagonists, which are effective for preventive as well as acute treatment of migraine.
- In order to prevent the development of MOH, most acute medications should be limited to less than 10 days per month, and preventive therapies should be used as the mainstay in patients with frequent headaches.

Choice of triptan

- Consider the length of the attack , the speed of onset of attack and formulary preference.
- Patients who do not respond well to one triptan may respond to another.
- The highest likelihood of consistent success has been found with rizatriptan(10 mg), eletriptan(80 mg), and almotriptan(12.5 mg).
- A meta-analysis suggested that eletriptan is the most likely of all the triptans to produce short-term and sustained benefit.
- Eletriptan and rizatriptan had the largest effect on 24-h sustained pain freedom among monotherapies at 33% and 24%, respectively.
- Sumatriptan, almotriptan, and zolmitriptan are very similar orally, while naratriptan and frovatriptan are slower in onset and have lower efficacy.
- The dose of rizatriptan must be adjusted downward in patients who take propranolol , since propranolol increases rizatriptan levels by 70 percent.

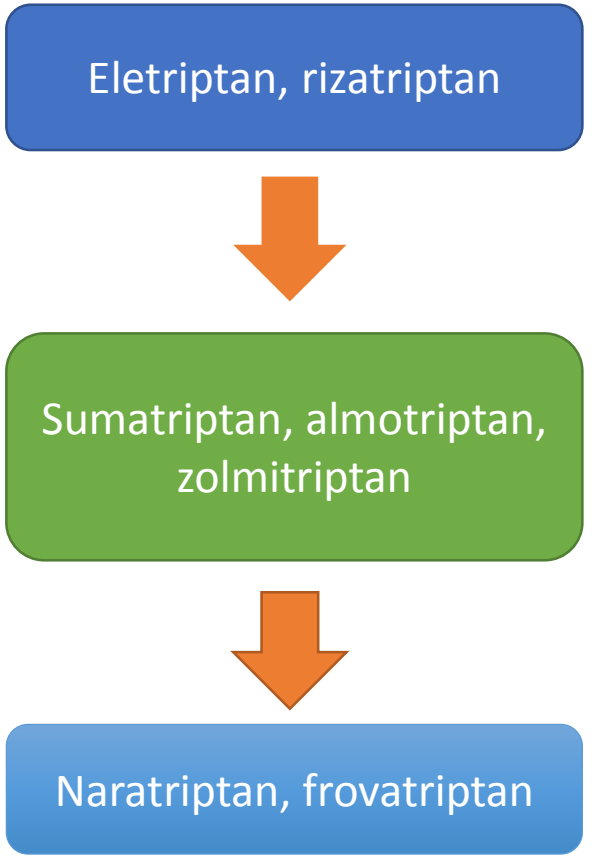
Triptan	Route (preparations)	Typical initial dose	Maxi dose per 24 hours	Notes
Sumatriptan	Oral (tablet)	50 to 100 mg	200 mg	The dose may be repeated once after two hours if needed.
	SUBQ (solution for injection)	6 mg	12 mg	More efficacious and faster than oral route with greater adverse effects May 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
	Spray (Imitrex and generics)	20 mg in one nostril	40 mg	The dose may be repeated once after two hours. The most common side effect is an unpleasant taste.
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

Triptan	Route (preparations)	Typical initial dose	Maxi dose per 24 hours	Notes
Eletriptan	Oral (tablet)	20 to 40 mg	80 mg	40 mg dose is recommended due to greater efficacy, 20 mg may be better tolerated. Metabolized by CYP3A4; do not use within 72 hours 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 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

Choice of triptan

Efficacy of triptans for pain freedom at 2 hours

Triptan, standard dose	Pain Freedom at 2 Hours (%)
Almotriptan, 12.5 mg	25
Eletriptan, 40 mg	39
Frovatriptan, 2.5 mg	35
Naratriptan, 2.5 mg	18
Rizatriptan, 10 mg	37
Sumatriptan, 50 mg	28
Zolmitriptan, 2.5 mg	27



Limitations of triptan

- All triptans should be limited to no more than 10 days of use per month to avoid MOH.
- It is still recommended that triptans be avoided in patients with hemiplegic migraine, basilar migraine, ischemic stroke, ischemic heart disease, Prinzmetal's angina, uncontrolled hypertension, severe hepatic impairment, or ischemic bowel disease.
- Combination with MAO 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.
- Eletriptan is primarily metabolized by cytochrome P-450 enzyme CYP3A4. Therefore, it should not be used within at least 72 hours of treatment with other drugs that are potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and nefazodone.
- 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.

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LASMIDITAN

- A selective serotonin 1F receptor agonist that lacks vasoconstrictor activity and can be used for patients with relative contraindications to triptans due to cardiovascular risk factors.
- FDA approval for acute treatment of migraine in adults in October 2019.
- The initial dose of lasmiditan is 50 or 100mg; 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.
- Lasmiditan may be considered for a patient who has inadequate response to or contraindication to a triptan.
- It may also be beneficial for people who have migraine onset later in the day or may choose to use lasmiditan before sleep as it may carry a sedating effect for a small portion of patients.

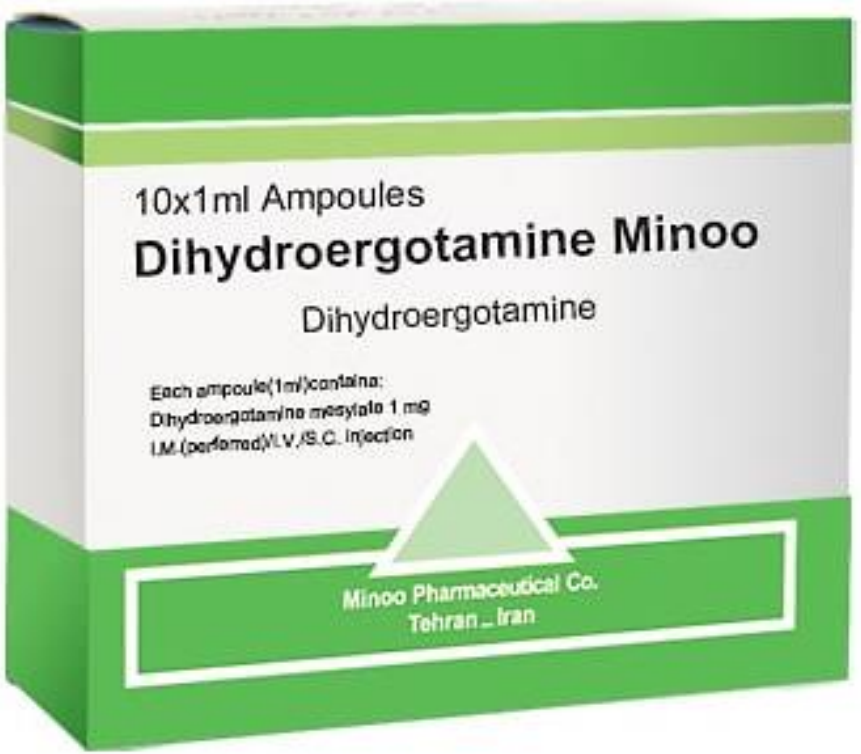
LASMIDITAN

- The most common adverse event is dizziness.
- Other relatively frequent adverse events are paresthesia, somnolence, fatigue, and nausea.
- Dizziness is dose-dependent and largely mild to moderate in severity, with a median duration of 1.5 to 2 hours.
- 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.
- It may cause medication-overuse headache; long-term safety study did not evaluate more than four doses of lasmiditan per month.

CGRP ANTAGONISTS

- Small-molecule CGRP antagonists (gepants) are oral options available for the acute treatment of migraine in patients with either insufficient response or contraindication to treatment with triptans.
  - ❑Ubrogepant 50 to 100 mg orally, may repeat dose in two hours; maximum dose 200 mg per 24 hours
    - ✓FDA approval for acute migraine in adults in December 2019
    - ✓The most common adverse events: nausea, somnolence, and dry mouth.
    - ✓No safety signals or side effects when used for up to eight doses per month.
  - ❑Rimegepant 75 mg as a single oral dose
    - ✓Similar FDA approval in February 2020
    - ✓Side effects: nausea and hypersensitivity reactions.
    - ✓No safety signals or side effects when used for up to 15 doses per month.
  - ❑Zavegepant 10 mg given intranasally as a single spray
    - ✓Nasal administration provides rapid absorption and may be preferred for patients with nausea and/or vomiting who are unable to tolerate oral options.
    - ✓FDA approved in 2023
    - ✓Adverse events are transient and mild including dysgeusia and nasal discomfort.

- CGRP receptor antagonists do not cause vasoconstriction, theoretically making it safe to use in people with stable cardiovascular disease.
- Gepants have not been studied in people who had a recent (within 6 months) vascular event.
- Therefore, consider using gepants with caution in individuals at high risk of cerebrovascular events, such as those with recent stroke.
- As blocking CGRP can reduce migraine frequency, gepants may not cause MOH, and neither ubrogepant nor rimegepant have an MOH warning on their label.
- Rimegepant has been found to be effective in some patients who did not respond previously to a triptan, but the efficacy of CGRP antagonists compared with triptans is not yet known.
- The safety of using a CGRP antagonist within two to four hours of a triptan or ergotamine agent is not well established.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ERGOTS

- Both ergotamine and DHE bind to 5HT 1b/d receptors.
- DHE is an alpha-adrenergic agonist that is a weaker arterial vasoconstrictor and more potent venoconstrictor than ergotamine.
- Parenteral DHE is effective for acute migraine, while the effectiveness of ergotamine is uncertain.
- DHE has fewer side effects than ergotamine.
- It is often used in combination with an antiemetic drug.
- Self-administered intranasal DHE has been found to be efficacious for the treatment of migraine symptoms.
- Subcutaneous DHE may be slightly more effective than the intranasal preparation. Its pain relief is longer and recurrence rate lower than SC Sumatriptan.

Ergotamine

- Oral and rectal ergotamine have a very poor bioavailability and most placebo-controlled trials of oral ergotamine alone have failed to show efficacy in the relief of migraine.
- It is unclear if it is the ergotamine itself or the other ingredients in the combination drugs that provide the most effect.
- 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.
- Ergotamine is the drug of choice in relatively few patients with migraine because of issues of efficacy and side effects.
- Suitable candidates may be those with prolonged duration of attacks (eg, greater than 48 hours) and possibly frequent headache recurrence.

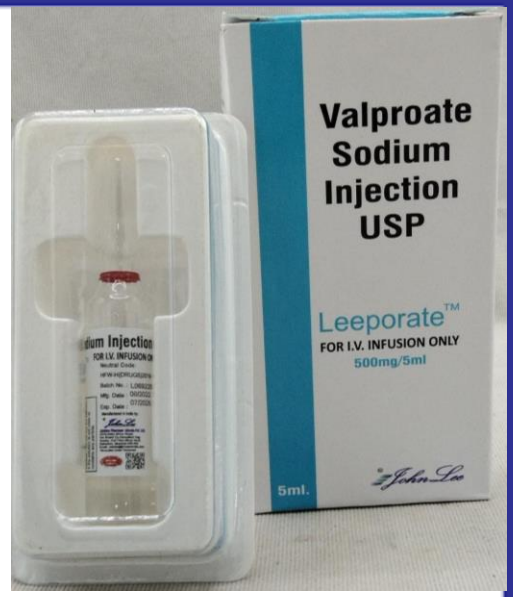
Ergots limitations

- DHE should not be used within 24 hours of triptans or other ergot-like agents.
- DHE 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, migraine with brainstem aura and migraine with prolonged aura.
- Ergots should be avoided in patients with coronary artery disease, peripheral vascular disease, hypertension, liver or kidney disease, and in pregnancy .
- Ergotamine overuse has been associated with an increased risk of cerebrovascular, cardiovascular, and peripheral ischemic complications, particularly among those using cardiovascular drugs.
- Years of use also may be associated with valvular heart disease.

PARENTERAL DEXAMETHASONE

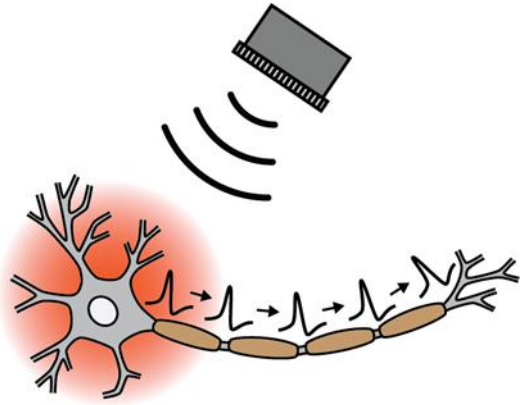
- Adjunctive treatment with a single dose of parenteral dexamethasone (10 to 24 mg) is recommended to reduce the risk of early headache recurrence for patients who are treated with standard abortive therapy for migraine headache in the emergency department or clinic.
- However, frequent use of adjunctive dexamethasone for headache increases the risk of glucocorticoid toxicity and should be avoided.

SODIUM VALPROATE

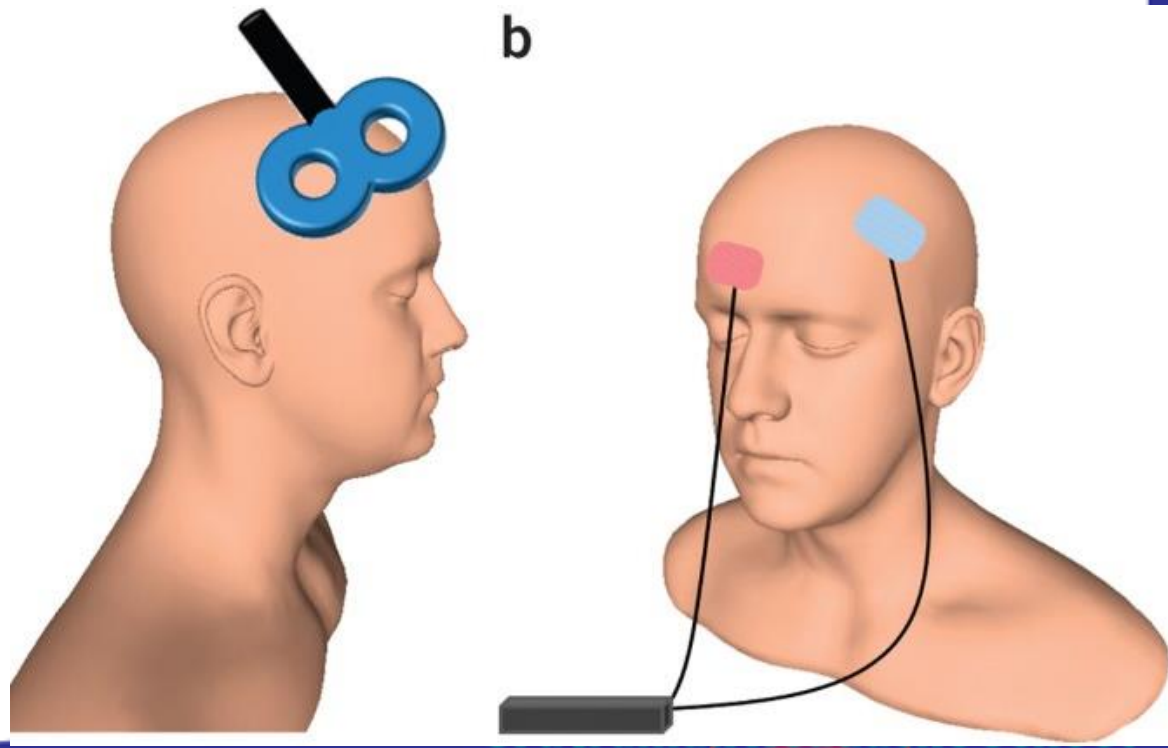


- Limited data suggest that IV sodium valproate may be effective for acute migraine treatment.
- Benefit has been found in small studies when sodium valproate was compared with ibuprofen, sumatriptan and dexamethasone.
- IV valproate is preferred over oral formulations for acute migraine treatment because 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



- These treatments stimulate the central or peripheral nervous system with an electrical current or a magnetic field.
- They are options for patients who prefer non-pharmacologic treatments or who have an inadequate response, inability to tolerate, or contraindications to drug treatments for migraine.

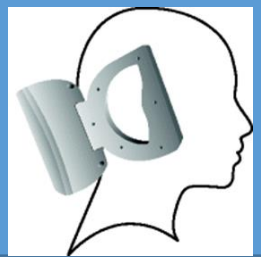


NEUROMODULATION

Four noninvasive neuromodulation devices have been studied and cleared by the FDA for treatment of acute migraine attacks:

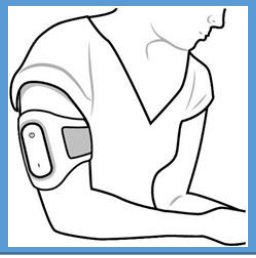
External trigeminal nerve stimulation

single-pulse transcranial magnetic stimulation



noninvasive vagus nerve stimulation

remote electrical neuromodulation



Transcutaneous supraorbital nerve stimulation

Dosing: 1 hour during migraine attack

Side effects: Paresthesia

Remote electrical neuromodulation

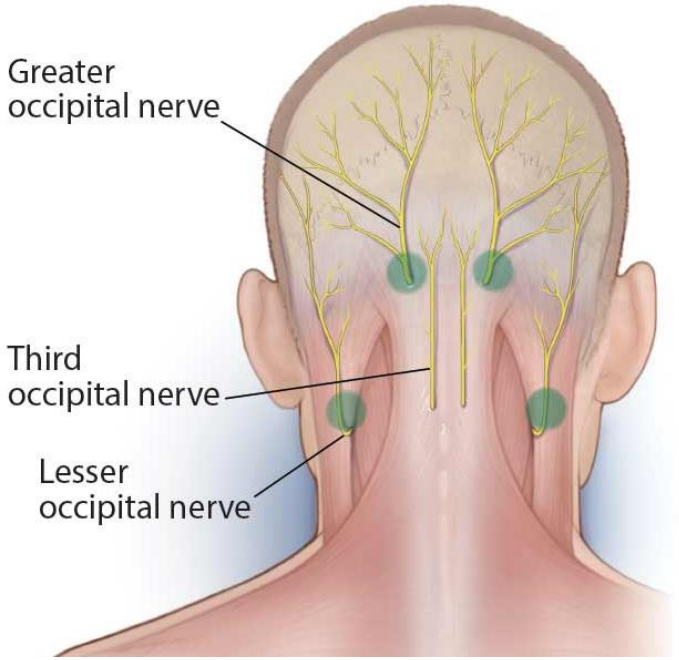
- A device applying non-painful electrical skin stimulation can reduce acute migraine pain.
- The armband is applied, and stimulation started as soon as possible after the onset of a migraine attack.
- Dosing: To upper arm for 45 minutes within 1 hour of onset; increase stimulation until perceptible but nonpainful.
- Mild device-associated adverse events in approximately 4 percent including 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.

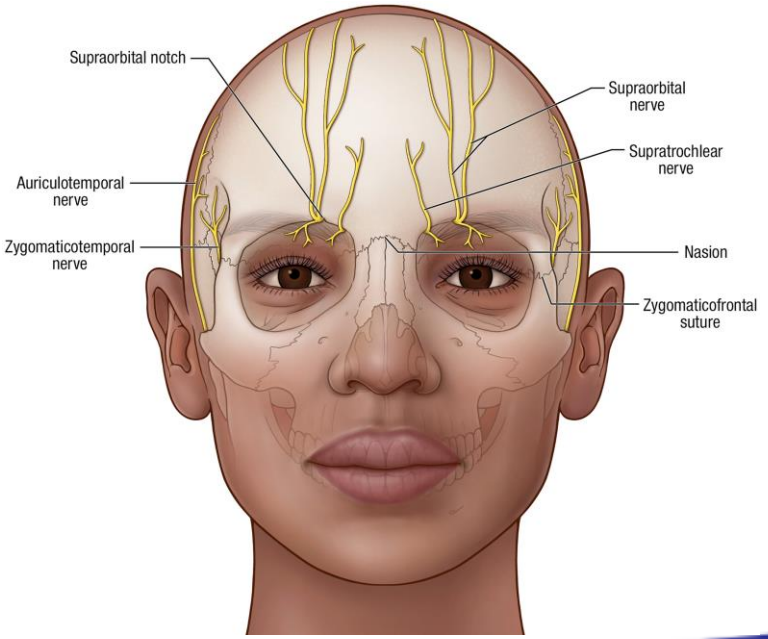
Transcranial magnetic stimulation(TMS)

- The efficacy of single-pulse TMS has been demonstrated in adults with episodic migraine with aura treated during the aura phase.
- The TMS device may prove to be useful as a second-line intervention for migraine patients who do not respond to first-line therapy with triptans or other agents or who are unable to take these agents because of contraindications or intolerance.
- The portable TMS device is available in the United Kingdom and the United States.
- TMS should not be used in patients who have epilepsy, since there is theoretical concern that TMS could trigger seizures.
- Dosing: Three pulses up to 3 times per attack as needed
- Side effects: Transient warmth, redness, or tingling sensation

Noninvasive vagus nerve stimulation(nVNS)

- nVNS may be beneficial for the acute treatment of episodic migraine.
- The most common adverse effects are discomfort at the application site and nasopharyngitis.
- Dosing: Bilateral 120 seconds to right and left of neck within 20minutes of onset of attack; repeat once after 15 minutes
- Side effects: Application site discomfort, nasopharyngitis





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.
- The most important contraindications to peripheral nerve blocks include known allergy to a local anesthetic, open skull defect, and overlying skin infection.

Conclusion

- Effective acute treatment requires the clinician to assess the patient, make a positive diagnosis, and then offer individualized therapy based on the patient's medical history, comorbidities, and preferences.
- Suboptimal or less effective treatment can lead to pain for a longer amount of time; chronification of migraine; more likelihood to have another attack; and increased risk for MOH.
- It is important to consider the role of preventive therapy when a patient is consistently experiencing a suboptimal response to acute treatment or is requiring frequent use of their acute treatment.

Thanks for your attention

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