Acute Migraine Treatment

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Mo Levin Disclosures

Consulting
Allergan
Supernus
Amgen
Lilly

Royalties
Oxford University Press
Anadem Press
Castle Connolly Med. Publishing
Wiley Blackwell
Mo Levin Disclosures

Off label uses of medication
DHE
Antiemetics
Zolmitriptan
Case

27 y/o woman has suffered ever since she can remember from “sick headaches”

- Pain is frontal, increases over time and is generally accompanied by nausea and vomiting. She feels depressed.
- The headache lasts the rest of the day but after sleeping through the night she awakens asymptomatic
1. Diagnosis
2. Severe Headache relief

What Does the Headache Patient Want?

Russell C. Packard, M.D.
Reprint requests to: Russell C. Packard, M.D., Neurology Service, U.S. Naval Aerospace Regional Medical Center, Pensacola, Florida 32512.

Accepted for Publication: February 12, 1979

SYNOPSIS

A survey was circulated among 100 outpatients with headache and 50 physicians to explore the question of what the headache patient wants when he comes to the doctor. Factors considered "most important to the patient" were rated by both physicians and patients. Other information obtained from patients included: age, sex, duration of headache(s), whether there was more than one type of headache, did they understand the cause of the headache, how much they believed "tension" contributed to their headache, whether they were concerned about a brain tumor, and expectations about pain relief.

Factors of importance to patients were listed as to those chosen first (most important), and as to their frequency of appearance among the top three choices. Pain relief and an explanation of what was causing the pain were listed with high frequency among both physician and patient groups. However, physicians tended to rate pain relief and medications higher (98% and 68%, respectively) than did the patients (69% and 20% respectively). Of factors selected first, 66% of physicians thought patients were primarily seeking pain relief, but only 31% of the patients listed pain relief as most important; 46% desired an explanation of the cause. One out of five patients chose factors not selected at all by physicians, such as a neurologic exam, an eye exam, or a doctor willing to follow them for their headache.

From this study it is concluded that although pain relief is an important aspect of treatment, it is often not the primary concern of the headache patient.

(Headache 19:370-374, 1979)
Diagnosis:
What do we need to beware of?

- Misdiagnosis of primary headache
- Secondary causes of headache
Red Flags in HA

- New *(recent onset or change in pattern)*
- Effort or Positional
- Later onset than usual *(middle age or later)*
- Meningismus, Febrile
- AIDS, Cancer or other known Systemic illness -
- Neurological or psych symptoms or signs
Basic principles of Acute Therapy of Headaches

- Diagnose properly, including comorbid conditions
- Stratify therapy rather than treat in steps
- Treat early
- Limit analgesics/abortives to avoid medication overuse headache
- Consider combining classes of medication (e.g. triptan+NSAID)
- Use non-pharmacological approaches – cold, quiet, relaxation
Acute Migraine - Medication options

**Non-specific**
- Acetaminophen
- OTC combinations with or without caffeine
- NSAIDs
- Neuroleptics – DA agonists
- Opioids
  - (Isometheptine)
  - (Butalbital and prescription combinations)

**Specific:**
- Triptans
- Ergots
# Acute Migraine - Tx options

<table>
<thead>
<tr>
<th>Non-specific</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Tylenol</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>Anaprox, Alleve</td>
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<tr>
<td>Indomethacin</td>
<td>Indocin</td>
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<tr>
<td>Ketorolac</td>
<td>Toradol</td>
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<tr>
<td>Metoclopramide</td>
<td>Reglan</td>
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<td>Domperidone</td>
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<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Stadol</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Vicodin</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Demerol</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
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</tbody>
</table>
NSAIDs

- Diclofenac, Flurbiprofen, Ibuprofen, Naproxen sodium, Piroxicam, and Tolfenamic acid have been shown to be effective

- Mechanism – COX inhibitors which block the production of Prostaglandins which mediate pain and inflammation.

- AEs – GI effects (due mostly to COX I blocking actions), platelet dysfunction, renal and hepatic effects, anaphylaxis-like effects

- Contraindications – Ulcers, Renal failure, bleeding diathesis, perioperatively
NSAIDs - Good choices and doses:

- **Oral:**
  - Ibuprofen 400-800 mg
  - Naproxen sodium 440-550

- **IM:**
  - Ketorolac 30-60 mg

- **IV:**
  - Ketorolac 15-30 mg

- **Rectally:**
  - Indomethacin 50 mg

- **Seltzer**
  - Diclofenac (Cambia)
What about OTC combinations?

What about OTC combinations?

Neuroleptic/antiemetics

• Analgesic mechanism – Unknown how dopamine antagonism helps to relieve migraine

• AEs – dystonia (preventable with diphenhydramine 25 mg IM (Benadryl) or benztropine (Cogentin)), akathisia, orthostasis, sedation, cardiac conduction changes.

• Doses –
  - Chlorpromazine 25-50 mg IV, pr
  - Prochlorperazine 25 mg IV, pr
  - Metoclopramide 10 mg IM, IV
  - Domperidone 10 mg po
Opioids

“Of the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and efficacious as opium”

Thomas Sydenham 1624-1689

- Mechanism – activation of mu opioid receptors
- Adverse effects – cough suppression, constipation, urinary retention, nausea, edema, seizures, pruritis, dependence
Other common anti-headache medications

• **Butalbital** – barbiturate  
  (Fioricet®, with caffeine and acetaminophen)

• **Isomethoventine** – a sympathomimetic  
  (in Midrin® with dichlorphenazone (antipyrene, an NSAID + chloral hydrate) and acetaminophen)

• **Combination analgesics**  
  Excedrin (ASA, acetaminophen, caffeine)  
  Anacin – ASA+caffeine
Acute tx of Migraine – limitations

Non-specific Tx (analgesia, sedation)

Simple analgesics and combo: ASA, acetaminophen, caffeine

NSAIDs
- Indomethacin, Ketorolac
- Ibuprofen, Naproxen

Comb meds
- Butalbital, sedatives

Opioids
- Oxycodone, Hydrocodone

Neuroleptics, antiemetics
- Prochlorperazine (Compazine®)
- Chlorpromazine (Thorazine ®).

← GI effects, liver tox
← GI effects, renal tox
← Addiction, sedation
← Addiction
← Dystonia, Akathisia, QT prolongation
# Acute Migraine - Medication options

**Non-specific**
- Acetaminophen
- OTC combinations with or without caffeine
- NSAIDs
- Neuroleptics – DA agonists
- Opioids
  - (Isomethptine)
  - (Butalbital and prescription combinations)

**Specific:**
- Triptans
- Ergots
# Acute tx of Migraine - options

## Specific Tx – triptans and ergots

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Imitrex</td>
<td>6mg IM, 20 NS, 50-100 po</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Amerge</td>
<td>2.5 po</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>10 mg po</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig</td>
<td>2.5-5 mg po, NS</td>
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<tr>
<td>Almotriptan</td>
<td>Axert</td>
<td>12.5 mg po</td>
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<tr>
<td>Frovatriptan</td>
<td>Frova</td>
<td>2.5 mg po</td>
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<tr>
<td>Eletriptan</td>
<td>Relpax</td>
<td>40-80 mg po</td>
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<tr>
<td>Dihydroergotamine</td>
<td>Migranal</td>
<td>1 mg IV, IM; 2-3mg NS</td>
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<tr>
<td>Ergotamine tartrate</td>
<td>Cafergpt</td>
<td>1-2 mg po, pr</td>
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</table>
Triptans

- Mechanism – Serotonin 1B and 1D agonists
- Efficacy - 70% improvement in 2 hours
- AE’s - chest tightness, sedation, nausea
- Contraindications – because of their vasoconstrictive effects: Coronary or cerebrovascular disease
## Triptan Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>( t_{1/2} ) (h)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>Biologic ( t_{1/2} )</th>
<th>Before Attack (%)</th>
<th>During Attack (%)</th>
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<tbody>
<tr>
<td>Sumatriptan</td>
<td>2</td>
<td>2</td>
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<tr>
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<td>Naratriptan</td>
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<tr>
<td>Rizatriptan</td>
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<td>1-1.5</td>
<td>42</td>
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<tr>
<td>Eletriptan</td>
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<td>1</td>
<td>2.8</td>
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<tr>
<td>Frovatriptan</td>
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<td>3</td>
<td>3</td>
<td>30</td>
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<tr>
<td>Almotriptan</td>
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<td>1.5</td>
<td>?</td>
<td>70</td>
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</table>
## Triptan Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>t₁/₂ (h)</th>
<th>Attack Before</th>
<th>Attack During</th>
<th>Activity (%)</th>
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<tr>
<td>Sumatriptan</td>
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Common Triptan AE’s and contraindications

- Tingling
- Warmth
- Flushing
- Chest discomfort
- Dizziness, somnolence
- HA recurrence
Common Triptan AE’s and contraindications

<table>
<thead>
<tr>
<th>Common AE’s</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>Tingling</td>
<td>Cardiovascular or Cerebrovasc disease</td>
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<tr>
<td>Warmth</td>
<td>Hemiplegic or ‘basilar migraine’</td>
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<tr>
<td>Flushing</td>
<td>Uncontrolled hypertension</td>
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<tr>
<td>Chest discomfort</td>
<td>Use within 24 hours of an ergot</td>
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<tr>
<td>Dizziness, somnolence</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>HA recurrence</td>
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</tbody>
</table>
Triptans

1. Contraindicated in cerebrovascular and cardiovascular disease
2. Contraindicated in pregnancy
3. Cause serotonin syndrome
4. Work best if taken early
5. If one doesn’t work, try another
6. All good - no best triptan
7. Triptans do not cause MOH
8. Triptans are the best acute Rx
9. Triptans are not good for children
Should triptans be avoided in patients with cardio/periph/cerebrovascular disease? Should they be avoided in patients with risk factors?


Evidence ... suggests that intense consumption of ergotamines may be associated with an increased risk of serious ischemic complications. As for triptans, available studies do not suggest strong CV safety issues.
Are triptans safe in pregnancy?

Pregnancy category C

The use of triptans during pregnancy does not appear to increase the rates for Major congenital malformations or prematurity. The increased rates of spontaneous abortions in the triptan-exposed group (OR=3.5) .... require further research.
Triptans do not cause 5HT synd
Theory – SS caused by increased activity at 5HT1A and 5HT 2A receptors; Triptans – 1B and 1D
Liver Enzyme system inhibitors can elevate triptan levels and T ½: cimetadine, antipsychotics, SSRIs, venlafaxine, antibiotics, antifungals, chemotherapeutic meds, protease inhibitor(antivirals).

<table>
<thead>
<tr>
<th></th>
<th>suma</th>
<th>zolmi</th>
<th>riza</th>
<th>nara</th>
<th>almo</th>
<th>frova</th>
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<td>*</td>
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<td>*</td>
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<tr>
<td>Concomitant MAO Inhibitors</td>
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<tr>
<td>Sulfonamide sensitivity</td>
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</tbody>
</table>
Triptans – pharmacological tidbits to know

Triptans without sulfa – riza, frova and zolmi
Rizatrip levels increased by propranololol (use ½ dose)
Nara clearance decreased by OCP
Frova and Ele are best in renal insufficiency
Triptans that are metab by MAO (Suma, Zolmi, Riza) cannot be given with MAO inhibs like phenelzine
HIV meds (protease inhibitors) suppress hepatic metab of eletrip and ergots

Conclusion – if pt getting excessive triptan symptoms, can change triptan – OR lower dose if suspect MMI
‘Best’ Triptan


Metaanalysis of 74 randomized clinical trials.

Results:
All triptans were significantly superior to placebo for all outcomes, with the exception of naratriptan for 24-hour sustained pain-free response.

**Eletriptan consistently yielded the highest treatment effect estimates.** For the two-hour endpoints, eletriptan was statistically significantly superior to sumatriptan, almotriptan, naratriptan, and frovatriptan for at least one of the two outcomes. Rizatriptan yielded the second highest treatment effects followed by zolmitriptan. For the 24-hour endpoints, eletriptan was statistically significantly superior to sumatriptan, rizatriptan, almotriptan, and naratriptan for at least one of the two outcomes.
Switching triptans

If one triptan fails, second/third choice may be effective.

Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan

M Färkkilä¹, J Olesen², C Dahlöf³, LJ Stovner⁴, JP ter Bruggen⁵, S Rasmussen⁶, N Muirhead⁶ & C Sikes⁶
¹Helsinki Headache Centre, Helsinki, Finland, ²KAS, Glostrup, Denmark, ³Migränklinik-Göteborg, Gothenburg, Sweden, ⁴Nevrologisk Afdeling RIT, Trondheim, Norway, ⁵Jeroen Bosch Hospital, Hertogenbosch, the Netherlands, and ⁶Pfizer, New York, USA

Cephalalgia

Early treatment with triptans

• The earlier the treatment, the more likely to achieve results


• Scholpp, J, et al. Early Treatment of a Migraine Attack while Pain is Still Mild Increases the Efficacy of Sumatriptan *Cephalalgia* 2004 24: 925-933
8.2 Medication-overuse headache

8.2.1  Ergotamine-overuse headache
8.2.2  Triptan-overuse headache
8.2.3  Analgesic-overuse headache
8.2.4  Opioid-overuse headache
8.2.5  Combination analgesic-overuse headache
8.2.6  Medication-overuse headache attributed to combination of acute medications
8.2.7  Headache attributed to other MO
Does overuse of triptan medication really cause MOH?

- Yes.
  - Pathophysiology of medication overuse headache: Insights and hypotheses from preclinical studies *Cephalalgia* 2011 31:851-860
  - Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people *Cephalalgia* 2011 31: 943-952
Triptans for children and adolescents

- Rizatriptan >6 y/o
- Almotriptan >12 y/o
- Zomig NS >12
- Treximet® >12
Ergotamine and DHE

- **Mechanism** – Broad range of receptor affinity including serotonin1B and 1D agonism with suppression of inflammation & vasodilation
- **Efficacy** – Good, particularly IV DHE
- **Duration** – DHE $T\frac{1}{2} = 10$ h
- **AE’s** – vasoconstrict, chest tightness, sedation, nausea
- **Contraindication** – Coronary artery disease
- **DHE available only in IV and nasal spray forms**
2015 Acute Migraine Guidelines

American Headache Society Evidence Assessment

Similar to 2000 guidelines with some reclassifications – Evidence grades A,B,C

- Acetaminophen and combinations
- Selected NSAIDs
- Triptans
- DHE
- Selected opioids – butorphanol, codeine
- Selected neuroleptics
- Isometheptine
2015 Acute Headache Treatment Evidence Review

• Level A evidence - effective
  – Acetaminophen,
    Acetaminophen+ASA+Caffeine
  – DHE NS or pulmonary
  – NSAIDs – ASA, Diclofenac, Ibuprofen, Naproxen
  – Opioids – Butorphanol NS
  – Triptans - all
2015 Acute Headache Treatment Evidence Review

• Level B evidence – probably effective
  – Neuroleptic antiemetics – Chlorpromazine IV, Promethazine IV, Metoclopramide IV, Prochlorperazine IV,IM,PR
  – DHE
  – Ergotamine+caffeine
  – NSAIDs – Flurbiprofen, Ketoprofen
  – Magnesium sulfate IV
  – Codeine + acetaminophen
  – Tramadol +acetaminophen
2015 Acute Headache Treatment Evidence Review

• Level C evidence – possibly effective
  – Valproate IV
  – Ergotamine
  – Decadron
  – Opioids
  – Butalbital
  – Lidocaine - intranasal
2015 Acute Headache Treatment Evidence Review – How to apply

- Pringsheim, Davenport, Marmura, Schwedt, Silberstein
"Must offer" (no options were suggested),
"Should offer" (IV metoclopramide, IV prochlorperazine and SC sumatriptan)
"May offer" (IV acetaminophen, IV aspirin, "parenteral" chlorpromazine, and a number of other parenteral agents including ketorolac (and some of which are rarely if ever used, like dexketoprofen, diclofenac, dipyrene, droperidol, haloperidol, and valproate).
Acute ED HA Treatment Evidence Review – Orr et al HEADACHE 2016

It also recommends corticosteroids for prevention of recurrence ("Should offer").

Injectable morphine and hydromorphone – “May avoid”
Shortcomings (typical for guidelines)

1. Old medications which were not extensively studied, are generally not recommended - e.g. the highly effective IV DHE failing to be recommended, and the lower-on-the-list placement of ketorolac and chlorpromazine both of which are used extensively and can be highly effective.
Shortcomings (typical for guidelines)

2. Some questionable practices are recommended because a study supported them - e.g. "Should offer" dexamethasone

3. Other considerations must be taken into account when choosing from available acute treatments for migraine – e.g. previous response history, comorbid conditions, and intolerable adverse effects in the past. Most guidelines do not address these.
Weighing the risks and benefits: 

Beneficial for acute migraine

- Acetaminophen and NSAIDs
- Combinations with caffeine
- Isomethoheptine
- Opioids in limited quantities
- Neuroleptic antiemetics with pretreatment
- Triptans
Weighing the risks and benefits:  

*Not beneficial for acute migraine*

- Butalbital + Aspirin + caffeine
- Corticosteroids
- Opioids
New treatment options for acute migraine treatment

• New forms of triptans & other older meds
• CGRP as a target
• Non-triptan serotonin agents
• Neuro”modulation”
New forms/routes for triptans

- Sumatriptan breath actuated nasal spray
- Onzetra Xsail
DHE Orally Inhaled

• Safe and effective in phase III study for migraine treatment.
• Effective in prolonged migraine and migraine with cutaneous allodynia
• Rejected 3 times by FDA due to manufacturing concerns - canister filling, uniformity of contents and actuation
Small molecule CGRP receptor antagonists

- Telcagepant – abandoned because of liver toxicity

- Ubrogepant – positive Phase II trials
A new class of triptans – Serotonin 1F receptor blockers - lasmiditan

Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study

Prof Markus Förkilä, MD, Prof Hans-Christoph Diener, MD, Prof Gilles Géraud, MD, Prof Miguel Láinez, MD, Prof Jean Schoenen, MD, Nadja Harner, MSc, Alison Pilgrim, BM, Dr Uwe Reuter, MD.
A new class of triptans – Serotonin 1F receptor blockers - lasmiditan

Phase 3 trials ongoing

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Lasmiditan</th>
<th>Triptans</th>
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<tbody>
<tr>
<td>Primary Site of Action</td>
<td>Trigeminal Pathway</td>
<td>Blood Vessels</td>
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<tr>
<td>Receptor</td>
<td>5-HT_{1F}</td>
<td>5-HT_{1B/1D}</td>
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<tr>
<td>CNS Penetrant</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Vasoconstrictor</td>
<td>No</td>
<td>Yes</td>
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</table>
Transcranial Magnetic stimulation (TMS)

• eNeura – FDA approved for migraine with aura

• Single pulse magnetic stimulation

VNS
– open label positive results only.
Other alternatives for acute HA treatment

- Intranasal lidocaine 4% (sphenopalatine ganglion blockade?)
- Occipital nerve blockade
- Valproate (Depacon®) - 500 mg IV
- Mg Sulfate - 1-4 g IV

Non-pharmacological treatment of acute headache

- Relaxation
- Cold or sometimes heat
- Massage
- Acupressure
- Aromatherapy
Nausea

- **Neuroleptic antinauseants – DA2 antag**
  - Promethazine (Phenergan ®) 25 mg po, PR, IV, IM
  - Prochlorperazine (Compazine ®) 5-10 mg po, PR, IV, IM
- **Ondansetron (Zofran ®) 5HT3 antag**
  - Oral 4-8 mg
  - Oral disintegrating 4-8 mg
  - IV - 0.15 mg/kg
- **Hydroxyzine – antihistamine**
  - 25-50 mg po, IV, IM
- **Aprepitant (Emend) – Subst P antagonist**
  - (neurokinin1 block)
  - 1 40 mg capsule $78; Dose 80 mg.
Antiemetic Treatment consideration

Long QT syndrome (LQTS): QTc longer than 0.44 seconds

1. Droperidol, Chlorpromazine, ondansetron (Zofran),
2. Lithium, Erythromycin, Venlafaxine (Effexor), Tizanidine (Zanaflex), quetiapine (Zyprexa), Cyclic antidepressants, Methadone
Non-pharmacological treatment of nausea

- Ginger
- Acupressure
Vertigo

• Antihistamines – Meclizine (Antivert), Dimenhydrinate (Dramamine), Diphenhydramine (Benadryl)
• Antiemetics – Prochlorperazine (Compazine), promethazine (Phenergan)
• Benzodiazepines – Diazepam, lorazepam, alprazolam, clonazepam
• Anticholinergics – Scopalamine transdermal patch
Why treatment of acute Migraine fails

- The diagnosis is incomplete or incorrect – secondary headache missed or wrong primary headache dx’d
- Important exacerbating factors have been missed: Medication overuse, caffeine overuse, dietary or lifestyle triggers, hormonal triggers, psychosocial factors, or the use of other medications that trigger headache
- Pharmacotherapy dose may be inadequate
- Route may be inappropriate
- Unrealistic, or escalating expectations.
Acute Headache Treatment
Final Tips & Pearls

- Careful diagnosis of HA and comorbid conditions
- Early treatment, with appropriate choice and doses
- Stratified care rather than treating in steps
- Nasal and injectable route for rapid or waking HA’s
- Avoid opioids, barbiturates, over-the-counter combinations
- Understand the range of possible MMI’s
- Utilize non-pharmacologic treatment, monitor success, and clarify expectations
- Avoid medication overuse