Diagnosis and Treatment of Severe Headaches

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Principles and Practice of Pain Medicine

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I.H.S. CLASSIFICATION OF HEADACHE I

1. Migraine
   - Without aura
   - With aura
   - Ophthalmoplegic
   - Retinal
   - Childhood periodic syndromes
   - Complications of Migraine

2. Tension-Type Headache
   - Episodic
   - Chronic

3. Cluster Headache
   - Cluster
   - Chronic Paroxysmal hemicrania

I.H.S. CLASSIFICATION OF HEADACHE II

4. Miscellaneous Headaches
   Unassociated With Structural Lesions
   - Headache associated with:
     - 5. Head trauma
     - 6. Vascular disorder
     - 7. Nonvascular intracranial disorder

5. Substances or their withdrawal
6. Noncephalic infection
7. Metabolic disorder
8. Disorder of facial or cranial structures
9. Cranial neuralgias, nerve trunk pain, and deafferentation pain
Common Benign Headache Syndromes

- Tension Type Headaches
- Migraine
- TMJ
- Sinus Headaches
- Cervicogenic Headaches
- Myofascial Pain with Headaches
- Cluster Headaches
- “Tic” Syndromes
- Indomethacin Responsive Headaches
- Occipital Neuralgia

Migraine Is One of Three Common Types of Headache

- Cluster
- Migraine
- Tension-type

Headache Prevalence

© Primary Care Network
Prevalence of Migraine
Age & Sex

- Peak prevalence at age 40 years
- Greatest impact on ages 25 to 55 years

Clinical Spectrum
- Neurologic
- Gastrointestinal
- Autonomic
- Musculoskeletal
- Mood
- Pain

Phases of a Migraine Attack
- Premonitory/Prodrome
- Aura
- Headache
- Postdrome
- Preheadache
- Headache
- Post-HA
Phase I — Prodrome

Common Symptoms
- Fatigue
- Mood change
- Cognitive change
- Food craving
- Muscle ache
- Yawning

Phase II — Aura

- Reversible focal neurologic disruptions
- Electrical vs vascular
- Visual, somatosensory
- Occur in only 15% of attacks

Phase III — Headache

Common Features
- 4 to 72 hours' duration
- Unilateral—60%
- Throbbing—60%
- Aggravated by activity
- Moderate-to-severe pain

Common Symptoms
- Nausea +/- vomiting
- Sensory disruption
- Cognitive slowing
- Musculoskeletal pain
- Hibernation (avoidance of stimulation)
Phase IV — Resolution

- Restoration of homeostatic balance
  - Vascular regulation
  - Reduction of inflammation
- Sleep or rest
- Sudden resolution
  - Vomiting
  - Powerful emotional experience

Risk Factors

- Hormones
- Chronobiologic changes
- Vasodilators
- Diet
- Drugs
- Sensory input
- Stress
- Trauma

Protective Factors

- Regular sleep
- Regular meals
- Regular exercise
- Biofeedback
- Healthy lifestyle
Migraine Transformation or Evolution

- Episodic Migraine
- Tension-Type Migraine
- Mixed Headache
- Chronic Daily Headache

MIGRAINE WITH AURA
- A. Headache pain is preceded by at least one of the following neurologic symptoms:
  - Sensory
    - Paresthesia
    - Numbness
    - Unilateral weakness
    - Speech disturbance (aphasia)
  - Visual
    - Scintillating Scotoma
    - Fortification Spectra
    - Photopsia
- B. No evidence of organic disease

MIGRAINE WITHOUT AURA
- At least five attacks fulfilling the following characteristics:
  - Duration of 4 to 72 hours
  - Headache with at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe intensity that inhibits or prohibits daily activities
    4. Aggravation by routine physical activity
Cortical spreading depression and trigeminal-parasympathetic link to meningeal vasodilation.

Cutaneous Allodynia and Migraine

- Allodynia: non-painful stimuli perceived as painful
- During a migraine attack
  - 9/42 (21%): no allodynia
  - 33/42 (79%): allodynia on ipsilateral to head pain
  - 28/42 (67%): secondary hyperalgesia and alldynia (outside of primary sensory field)
- Allodynic patients were older than those without allodynia (42:10 vs 34:5) and had more years of migraine
**Migraine:**
Trigeminovascular Inflammation, nociceptive pain, central sensitization and neuropathic pain

(Taken from Hargreaves, Shephard 1999)

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**TENSION-TYPE HEADACHE**

- Previously called tension headache, muscle-contraction headache, stress headache, and ordinary headache
- Most common types of headache
- Intensity of pain not as great as migraine headache

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**EPISODIC TENSION-TYPE HEADACHE**

- At least 10 previous headache episodes fulfilling the following diagnostic criteria:
  - Headache lasting from 30 minutes to 7 days
  - A minimum of two of the following pain characteristics:
    1. Pressing or tightening
    2. Mild or moderate intensity
    3. Bilateral location
    4. No aggravation upon physical activity
CHRONIC TENSION-TYPE HEADACHE

- Previously known as chronic daily headache
- Average headache frequency 15 days per month for 6 months or 180 days per year
- Frequently associated with analgesic overuse
- May have migrainous features superimposed intermittently

Diagnosis

- History is the most important tool to make diagnosis
- Neurologic and physical examination is normal
- Rule out curable causes
- Co-morbid conditions
- Diagnose, then treat

Headache History

How many major headache types?
- Age at onset
- Frequency
- Location
- Time from onset to peak intensity
- Associated symptoms
- Duration
- Aggravating and relieving factors
- Triggers
- Previous medications (dose, schedule, efficacy)
Headache History

- Do your headaches interfere with activities?
  - Do you miss work or school?
  - Do you work at a slowed pace?
  - Do you cancel social activities?
- How frequently do headaches occur?
- Is the headache pattern stable?
- How effective are your current treatment attempts?
- Comfort signs

SYMPTOMS AND SIGNS OF ORGANIC DISEASE ON PATIENT INTERVIEW

- Extremely rare
- Sudden onset of new severe headache or worst headache ever experienced
- Progressively worsening headaches
- Onset of headache with exertion, coughing, straining, or sexual activity
- Drowsiness, confusion, or memory loss

SYMPTOMS AND SIGNS OF ORGANIC DISEASE ON PATIENT INTERVIEW

- Chronic malaise, myalgia, or arthralgia
- Fever
- Progressive visual disturbance
- Weakness, clumsiness, or loss of balance
- First headache after 50 years of age
SYMPTOMS AND SIGNS OF ORGANIC DISEASE ON PATIENT EXAMINATION

- Abnormal vital signs (fever, hypertension)
- Altered consciousness or cognition
- Meningeal irritation ("stiff neck")
- Papilledema or hemorrhage of the ocular fundus
- Pupils unequal and/or poorly reactive
- Visual field deficit

SYMPTOMS AND SIGNS OF ORGANIC DISEASE ON PATIENT EXAM, con’t

- Tender, poorly pulsatile cranial arteries
- Weakness or sensory loss in face or limbs
- Clumsiness or loss of balance when standing or walking
- Reflex asymmetry or abnormal plantar response

Treatment Principles

- Diagnosis Based Treatment
- Consider Mechanisms
- Individualize Treatment Plan
- Recognition of Triggers
- Elimination of Triggers
- Review Treatment Options
- Review Expectations
- Reassurance
- Scan or Not to Scan?
Non-Pharmacological Treatments:

- Physical Therapy
- Manipulation
- Relaxation, Meditation
- Stress Management, Yoga
- Biofeedback
- Injection Therapy
- Acupuncture
- Actions to Promote Normal Sleep

Non-Pharmacological Therapies are Preferred When:

- During pregnancy
- When the patient:
  - is reluctant to initiate
  - poorly tolerant of
  - has contraindications to
  - has shown poor response to Drug treatment

Non-Pharmacological Treatments:

- Evidence is Best for:
  - Relaxation Therapy
  - Thermal Biofeedback with Relaxation Training
  - EMG Biofeedback
  - Cognitive Behavioral Therapy
- Evidence is Less Available /Convincing for:
  - Acupuncture, Homeopathy, Hypnosis, TENS, Cervical Manipulation, Hyperbaric Oxygen
Nutritional Supplements

- Most Commonly Used: Feverfew, Riboflavin, Magnesium, Herbal Remedies
- Mechanisms are unclear
- Side Effects: Less well known, include Diarrhea, Polyuria
- Neuropharmacology Principle

Pharmacologic Treatment

- Preventive
- Abortive
- Symptomatic
- Palliative

What is Prophylactic (Preventive) Treatment?

- An action taken to Decrease the Frequency and Severity of Migraine Attacks
- Pharmacological vs Non-pharmacological
- Usually taken on a daily basis for Weeks or Months, occasionally shorter courses
- Most are not potent analgesics
When is Prophylaxis Appropriate?

- Frequent Headaches (> 1 headache day/wk)
- When Attacks or Dread of Attacks interfere with normal range of activities
- Acute treatments are ineffective or contraindicated
- Prolonged Neurological Symptoms
- Hx. Of Migrainous Infarction

Reasonable Goals for Prophylaxis

- Decrease attack frequency by 50% or greater
- Improve responsiveness to Abortive treatment
- Improve the patient daily functioning and quality of life
- Avoid Significant Side Effects

Prophylactic Therapy: Basic Principles

- Taper off over-used acute treatments
- Start Low, Go Slow
- Stick with it, If tolerability is not an issue
- Monitor response to Treatment Objectively, but interpret response Subjectively
- Prophylaxis is NOT a Life Sentence
Selection of a Prophylactic Drug

- At present, Not Based on Comparative Trials
- Largely based on Co-morbid Conditions or Coexisting Therapies
- Try to Get Two for One
- Avoid Drug Interaction
- Pregnancy: Avoid Prophylaxis when possible

Medication With Proven Efficacy

- Methysergide
- Certain B-Blockers
- Divalproex Sodium
- Tricyclic Antidepressants
- Topiramate

Potential “Winners”

- Other Antidepressants?
- Gabapentin/Pregabalin
- Newer Antiepileptics
- Tizanidine
- Botulinum Toxins
- TPI’s
- GONB
Beta Adrenergic Blockers
- Most Commonly used: Propranolol, Nadolol, Timolol, Atenolol, Metoprolol
- All 5 lack Sympathomimetic activity
- Side Effects: Hypotension, Bradycardia, fatigue, dizziness, decreased bronchodilatory response, GI disturbance, depression, sleep or memory disturbances
- Contraindications: asthma, depression, CHF, peripheral vascular disease or brittle DM.

Tricyclic Antidepressants
- Commonly used: Amitriptyline (best evidence of efficacy), Nortriptyline, Imipramine, Desipramine
- Block reuptake of 5-HT & Norepinephrine, also has anti-NMDA activity
- Side effects: Sedation, dry mouth, tachycardia, weight gain, constipation & urinary retention
- Contraindications: Mania, glaucoma, cardiac arrhythmias and conduction defects, Sz D/O

Anti-convulsants
- Commonly used: Divalproex Sodium, Gabapentin, Topiramate
- Potentiate GABA, activation receptor by increasing endogenous GABA levels or non-benzodiazepine, non-barbiturate mechanisms
- Side effects: Appetite mod., hair loss (DV), sedation, cognitive probs, Dz., tremor, decr.platelet aggr., minor elevations in liver function tests, renal stones
**5-HT Antagonists, Agonists**

- Commonly Used: Methysergide, cyproheptadine
- Antagonists at 5HT₂ receptors 5-HT₂B probably most important
- Side effects: depression, edema, dizziness, sedation, Fibrotic complications, dry mouth, urinary retention, weight gain
- Contraindications: Heart disease, PVD, glaucoma, monoamine oxidase inhibitors

**Calcium Channel Blockers**

- Commonly used: Verapamil, Flunarizine
- Vasodilating, neuroprotective, FHM gene codes for a different Calcium Channel
- Side Effects: Hypotension, constipation, fatigue, nausea, edema & increased headache
- Contraindications: Cardiac Conduction Abn, Sick Sinus Syndrome, Bradycardia, concurrent use of Beta Blockers

**MAO INHIBITORS**

- Most often used: Phenelzine, Celegeline
- Mechanism: unknown, possible down regulation of 5-HT and adrenergic receptors
- Side Effects: Hypotension, Hypertensive Crisis, GI Disturbance, Ejaculation Failure
- Contraindications: pheochromocytoma; CHF, Abn.LFT’s, use of sympathomimetic drugs, intake of tyramine-containing foods
Cervicocranial Junction

- Cervicocranial Syndrome
- Intractable Daily Headache
- Basis for Injections, and Nerve Blocks
  - Occipital Nerve Blocks
  - Cervical MBBs
  - C 2 DRG Blocks, and RFT
  - Stimulation Therapies

Clinical Studies of BTX-A for Headaches

- Migraine
  - Chronic daily headache with migraine features
  - Klapper and Klapper, 1999
  - Chronic tension-type headache (CTTH)
  - Cervicogenic, Mixed
    - Relja, 1997; Relja, Koric, 1999
    - Freund, Schwartz, 2000 and Rollnik et al, 2000
  - Chronic Migraine
    - Dodick et al 2010 Pooled data from 2 large studies

Conclusions

- Prophylactic Treatment is often Necessary for Long term Improvement
- Methods of its Use Currently Based More on Clinical Judgement than on Clinical Trials
- Mechanisms of the Drugs are Complex and Incompletely Understood
- Side Effects Continue to be a Problem
Abortive Treatments

- Almost always indicated
- May prevent progression to chronic states

Medications Include
- Certain Anti-emetics
- NSAID’s
- Ergotamines
- Corticosteroids
- Major Tranquilizers
- 5-HT1 agonists

Migraine: Acute Treatment
Mild to Moderate Attacks

- Acetaminophen
- NSAID’s
  - Aspirin
  - Indomethacin
  - Naprosyn
  - Ketoprofen
  - Ibuprofen
- Isometheptene mucate

Nonsteroidal Anti-inflammatory Drugs

- Aspirin 900 - 1000 mg
- Naprosyn 500 - 750 mg
- Ketoprofen 50 - 150 mg
- Ibuprofen 1000-1200 mg

Adverse effects: GI irritation, prolonged bleeding times, tinnitus, renal nephropathy

Possible Mechanism: blocks cyclooxygenase
Isomethetepne mucate

- Combined with dichloralphenazone and acetaminophen
- Side effects: Sedation, dizziness, skin rash, rarely tachycardia
- Sympathomimetic amine, possesses both alpha and beta-adrenergic properties
- Possible mechanism: mildly vasoconstrictive

Butalbital

- 50 - 100 mg dose q 4-6 hrs
- Combined with caffeine and aspirin or acetaminophen
- Side effects: sedation, dizziness, nausea, habituation
- Used more than one day a week, dose escalation may become a problem
- Agonist at GABA<sub>A</sub> modulatory site

Migraine: Acute Treatment
Mod. To Severe Attacks

- Ergotamines
  - Rizatriptan
- Sumatriptan
  - Eletriptan
- Naratriptan
  - Frovatriptan
- Almotriptan
  - Zolmitriptan
Migraine: Acute Treatment
Severe Attacks

- Subcut. Sumatriptan
- IV or Subcut. DHE
- IV Chlorpromazine
- IV Droperidol
- IV Valproate

Migraine: Acute Treatment
During Pregnancy

- Therapeutic Options More Limited
- Mild: Acetaminophen
- Severe: Meperidine

Ergotamines/Dihydroergotamine

- Ergotamine
  - oral 0.6 - 1.0 mg
  - sublingual 2.0 mg
  - suppository 1.0 - 2.0 mg
- DHE (Migranal)
  - intranasal 0.5 - 1.0 mg
- Side effects: nausea, vomiting, tachycardia, chest pain, diarrhea
- Possible Mechanism: 5-HT_{1B} agonist
Headache Response Rate at 2 Hours (average from placebo-controlled acute studies)

- Eletriptan-80mg: 68%
- Naratriptan-2.5mg: 45%
- Rizatriptan-10mg: 65%
- Sumatriptan-100mg: 59%
- Zolmitriptan-2.5mg: 60%
- Almotriptan-12.5mg: 40%
- Frovatriptan-2.5mg: 0%

Average Headache Response at 2 hrs (%)

Sustained Headache Response

Sustained response = Headache Response at 2 hours and no recurrence by 24 hours and no use of rescue medication

- Eletriptan-40mg: 35%
- Eletriptan-80mg: 51%
- Naratriptan-2.5mg*: 57%
- Rizatriptan-10mg: 46%
- Sumatriptan-100mg: 40%
- Zolmitriptan-5mg: 38%
- Frovatriptan-2.5mg: 46%

Average sustained response (%)

* Data is based on sustained headache response at 4 hours instead of 2 hours

Intravenous DHE

- DHE 45 (1 mg SC, IM or IV)
- Combined with an antiemetic (metoclopramide 10 mg) for treatment of status migrainosus
- Side effects: nausea, vomiting, tachycardia, chest pain, diarrhea

DHE 45 (1 mg SC, IM or IV)

Combined with an antiemetic (metoclopramide 10 mg) for treatment of status migrainosus

Side effects: nausea, vomiting, tachycardia, chest pain, diarrhea
Intravenous Droperidol

- Droperidol 2.5 mg IV, may repeat q 30 min. x 2 if headache persists
- Should pretreat with Cogentin 1 mg po and the treat with 1 mg bid for two days to avoid akathisia or other extrapyramidal side effects

Wang et al., 1997

Intravenous Depakote

- Depakon (300-500 mg IV given over 15 to 30 seconds) has successfully treated acute prolonged migraine in two open trials (Edwards & Santaracangelo 1999; Kailasam et al., 1999)
- Should be infused rapidly (30 seconds)
- Also useful for rapid initiation of prophylaxis

Concurrent Use of Acute and Prophylactic Treatments

- Breakthrough attacks may occur despite Successful Preventative Treatment
- Overuse of Acute treatments seem to Undermine the Effectiveness of Both Acute and Prophylactic Therapies
- Interactions between Acute and Preventative therapies should be avoided
### Potential Interactions Between Acute and Prophylactic Treatment

<table>
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<th>COMBINATIONS WITH POTENTIAL RISK</th>
<th>Prophylactic</th>
<th>Acute Treatment</th>
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<tbody>
<tr>
<td>Methysergide</td>
<td>Ergots, Triptans</td>
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<tr>
<td>Propranolol</td>
<td>Rizatriptan (lower dose required)</td>
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<tr>
<td>MAOI's</td>
<td>Midrin, Triptans, Meperidine</td>
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<tr>
<td>NSAIDS</td>
<td>Other NSAIDS</td>
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<tr>
<td>Valproate</td>
<td>Butalbital (additive Sedation)</td>
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### Potential Interactions Between Acute and Prophylactic Treatment

- Anti-emetics
- Anxiolytics
- Muscle Relaxants
- Analgesics
  - NSAID's
  - Opioids
  - Barbiturates
  - Combination Analgesics

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### Conclusions

- Acute therapies have greatly improved over the past decade
- Acute treatments seem to be most effectively when applied “Hard, fast and infrequently”
Intractable Headaches
“Status Migrainosus”

- Combination Parenteral Drugs
- Suppositories
- IM Injections
- IV Infusions
  - Magnesium
  - Lidocaine
  - Droperidol
  - Ketamine
  - Propofol