

Preventive Treatment of Migraine

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Overview

- Not all migraine patients require preventive therapy
- Unfortunately many patients who are candidates are not offered therapy
- When to consider preventive therapy
- Goals of prevention
- General principles of therapy
- What agents are available
- How to optimize therapeutic outcomes

When to Consider Prevention

- Migraine that significantly interferes with the patient's daily routine despite acute treatment
 - two or more attacks a month that produce disability that lasts at least 3 days
 - headache attacks that are infrequent but produce profound disability
- Failure, contraindication to, or troublesome side-effects from acute medications
- Overuse of acute medications

Ramadan NM, et al. Evidenced-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. <http://www.neurology.org>. Silberstein SD & Goadsby PJ. *Cephalalgia* 2002;22:491–512.

When to Consider Prevention

- Special circumstances:
 - Hemiplegic migraine
 - Attacks with a risk of permanent neurological injury
 - During pregnancy:
 - Severe disabling attacks accompanied by nausea, vomiting, and possibly dehydration
- Very frequent headaches (more than two a week)
- Pattern of increasing attacks over time, with the risk of developing rebound headache with acute attack medicines
- Patient preference: the desire to have as few acute attacks as possible

Ramadan NM, et al. Evidenced-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. <http://www.neurology.org>.
Silberstein SD & Goadsby PJ. *Cephalalgia* 2002;22:491–512.
Silberstein SD. Migraine and pregnancy. *Neurologic Clinics* 1997; 15:209–31.

GOALS OF PREVENTIVE TREATMENT

- ▣ Decrease attack frequency (by 50%), intensity, and duration
- ▣ R_x Improve responsiveness to acute
- ▣ Improve function and decrease disability
- ▣ Intervene to prevent rebound

GENERAL PRINCIPLES OF PREVENTIVE TREATMENT

Start low and increase dose slowly

- Use long-acting formulation if compliance an issue

Adequate trial (2–3 months) at an appropriate dosage

Maximize treatment of comorbidity and avoid interfering and contraindicated medications

Evaluate therapy

- Use headache calendar (diary)
- Attempt to taper and discontinue treatment when headaches well controlled

PREVENTIVE MEDICATIONS: DRUG CLASSES

Antiepilepsy drugs
(AEDs)

Antidepressants

β -Blockers

Ca²⁺-Channel blockers

Serotonin antagonists

NSAIDs

Other

- Vitamins
- Minerals
- Herbs
- ACE/ARB Antagonists (lisinopril, candesartan, olmesartan)

Preventive Medications for Migraine-1

Antiepilepsy Drugs

- Divalproex sodium*
[Depakote]
500-1500 mg/d (Class A)
- Gabapentin [Neurontin]
900-~~2400~~ mg (Class B)
- Topiramate * [Topamax]
100 mg (Class A)
- Zonisimide 100-200 mg: No
evidence, but used
- Pregabalin 10:1 gabapentin to
pregab
No evidence but used
- Lamotrigine
Evidence for aura only

Other

- Chelated Magnesium
 - 400-600 mg/d (Class B)
- Vitamin B₂ (Riboflavin)
 - 25 mg vs 400 mg/d (Class B)
- **Butterbur /Petasites (Petadolex)**
 - 100-150 mg/d (Class B)
- Coenzyme Q10
 - 300 mg/d (Class B)
- Feverfew
 - 50- 82 mg/d (Class B)

* FDA approved

Preventive Medications for Migraine-2

Antidepressants

- **Tricyclics**
 - Amitriptyline
30-150- mg
(Class A evidence)
 - Nortriptyline, Doxepin
 - Protriptyline, Imipramine
(All Class C)
- **SNRIs**
 - **Venlafaxine 150 mg**
(Class B evidence)
- **MAOIs**
 - Phenelzine (Class C)
- **SSRIs**
 - Fluoxetine 10-40 mg (Class B)
 - Fluvoxamine, Paroxetine
 - Sertraline
(All Class C)

Antidepressants

- **Bupropion,**
- **Mirtazepine,**
- **Trazodone**
- **Venlafaxine**
(Class C)

* **FDA approved**

Preventive Medications for Migraine-3

Beta-blockers

- Propranolol*
60 – 160 mg QD (Class A)
- Nadolol (80-240 mg)
- Atenolol (100 mg)
- Metoprolol (200 mg)
(All Class B)
- Timolol*
20-30 mg/day (Class A)

Ca-channel Blockers

- Verapamil
240 mg/day (Class B)
- Diltiazem (Class B)
- Amlodipine (No RCTs)

Anti-serotonin Drugs

- Cyproheptadine
 - Class C
- Methylergonovine
 - Class C

* FDA approved

Antidepressants in migraine prevention

- TCAs are the standard, and great for sleep, neck pain, depression
- Side effects may be treatment limiting
 - Dry mouth, constipation, sedation & weight gain
- SSRIs are generally ineffective
- New data suggests 150 mg venlafaxine, an SNRI, is as effective as amitriptyline
- Consensus for MAOI effectiveness

Beta blockers in migraine

- Propranolol and timolol FDA approved
- Metoprolol may be Class A evidence as well
- Nadolol and atenolol widely used
- Contraindicated in DM, Raynauds, asthma, depression, hypotension
- Good for comorbid depression and hypertension

CCBs in migraine prevention

- Drugs of choice for hemiplegic migraine, and, possible basilar-type migraine
- Widely used in migraine with aura
- Class B evidence for verapamil and diltiazem
- Adverse events constipation, pedal edema, and hypotension
- Monitor with EKGs-1st degree heart block

Rationale for AEDs in Migraine Prevention

- Increasingly used for migraine prevention based on well-controlled clinical trials
- Multiple mechanisms of action for each drug
 - Stabilizing or modulating the excitability of the:
 - Trigeminal nucleus caudalis
 - Cortical neurons
- Divalproex and Topiramate act by:
 - Inhibiting the release or antagonizing the effect of glutamate
 - Potentiating GABA
 - Modulating sodium and calcium channels

Valproate in Migraine Prevention

- Received FDA indication for migraine prevention in 1996
- Proven effective in four double-blind, placebo-controlled trials
- Multicenter, double-blind, placebo-controlled trial of 12 weeks (N=176)
- Primary efficacy variable
 - 4-week migraine *attack* frequency during experimental phase
- Dosed at 125, 250, 500 mg to a maximum of 1,000 mg/day depending on formulation and severity of disease

Valproate: Safety Issues

- Black box warning
 - Hepatotoxicity (rare) – hepatic failure. Children < 2 years of age at risk
 - Teratogenicity – neural tube defects (1-2%)
 - Polycystic ovaries- 10% in 1st year
 - Pancreatitis (rare) – reported both in adults and children
- Thrombocytopenia
- Hyperammonemia
- Drug interactions due to metabolism via the cytochrome P450 enzyme system
- Pregnancy category D: not for use in pregnant women or those considering pregnancy

Topiramate in Migraine Prevention

- Received FDA indication for migraine prevention in August 2004
- Two 26-week, double-blind, placebo-controlled trials
 - MIGR-001 (N=469)
 - MIGR-002 (N=468)
- Patients randomized to receive placebo, or topiramate 50, 100, or 200 mg/day
 - 8-week titration of 25 mg/day to maintenance dose
 - 18-week maintenance phase
- Efficacy evaluations every 4 weeks

Brandes JL, et al. Topiramate for Migraine Prevention: A Randomized Controlled Trial. *JAMA*. 2004;291:965-973.

Silberstein SD, et al. Topiramate in Migraine Prevention: Results of a Large Controlled Trial. *Arch Neurol*. 2004;61:490-495.

Topiramate: Most Common Treatment-Emergent Adverse Events

	Placebo (n=445) %	TPM 50 mg/day (n=235) %	TPM 100 mg/day (n=386) %	TPM 200 mg/day (n=514) %
Paresthesia	6	35	51	49
Fatigue	11	14	15	19
Anorexia	6	9	15	14
Diarrhea	4	9	11	11
Weight decrease	1	6	9	11
Memory difficulty	2	7	7	11
Difficulty with concentration	2	3	6	10
Language problems	2	7	6	7
Hypoesthesia	2	6	7	8

TPM = topiramate.

***Incidence of the most common treatment-emergent AEs by double-blind data set: Studies MIGR-001, MIGR-002, MIGR-003, and CAPSS-155.**

Topamax® [package insert]. Raritan, NJ: OMP Division of Ortho-McNeil Pharmaceutical Inc; 2004

Topiramate: Other adverse events of concern

- Glaucoma
 - Can be after 6 months
 - Inflammatory angle change
 - Reversible
- Anhydrosis and hyperthermia
 - More common in young ages and high doses
- Hyperchloremic acidosis
- Nephrolithiasis
- Psychosis, increased anxiety or depression

Topiramate: Safety Issues

- Kidney stone incidence: ~1%
 - Hydration is recommended to reduce stone formation
- Rare adverse events include:
 - Inflammatory narrow angle-closure glaucoma
 - Oligohidrosis and hyperthermia
- Pregnancy category C
 - Data being collected in North American/European registries
- Topiramate has few drug-drug interactions

Tricks for treating with topiramate

- Half life is 25 hours: why not dose once at hs?
- In the Psychiatry literature (not in the Neurology literature), one article suggested lower rate of CNS side effects (psychosis) with slower titration rate
- In the regulatory trials it took 1 month at 100 mg to separate from placebo
- $\geq 50\%$ on 100 mg had $\geq 50\%$ reduction in migraine periods (days) at 3 months
- $\geq 50\%$ of the 50% had $\geq 75\%$ reduction at 3 months
- There was evidence for continued improvement over 6-10 months

Herbs, minerals vitamins and supplements

- B2 (25-400 mg), chelated magnesium (400-600 mg), coenzyme Q10 (300 mg), petasites (Brand name Petadolex) (150 mg) all have RCTs establishing Class B evidence for migraine prevention
- Magnesium can cause diarrhea
- CoQ10 can cause rash
- Petadolex can cause belching

GENERAL PRINCIPLES OF PREVENTIVE TREATMENT

Assess Coexisting Conditions

- Select drug to treat both disorders
- Do not use migraine drug if contraindicated for other condition
- Do not use drug for other condition that exacerbates migraine
- Be aware of drug interactions
- Special concern for women of childbearing potential- the OCP and divalproex issues

COMORBID AND COEXISTENT CONDITIONS

Coexistent disorders are commonly present

Therapeutic opportunities

- Treat two disorders with a single drug
 - Hypertension or angina—use β -blocker
 - Depression—use TCAs or MAOIs
 - Epilepsy or mania—use divalproex or topiramate

Therapeutic limitations

- Avoid β -blockers with depression, asthma, or hypotension

PREVENTIVE TREATMENT: USE OF ACUTE MEDICATION

Preventive treatment does not eliminate all attacks

Breakthrough attacks need treatment

Must use acute and preventive treatment together

- Limit acute drug use to prevent drug-induced headache
- Certain drugs require caution or cannot be used together
- Acute medications may have more benefit

Optimize Preventive Therapy With a Diary

- The basics:
 - Track headache frequency and severity
 - Record acute medications and response
 - Are we achieving our acute and preventive goals?
- Customize for individual patients:
 - Monitor nonpharmacological goals
 - e.g. exercise program, fluid intake, etc.
 - Track potential risk factors
 - Menstrual cycle

Tips On Using Preventives: Summary

- Start low, go slow (but not too slow), and build up to effective doses
- Consider comorbidity in agent selection
- Be vigilant for medication overuse
- Combining nonpharmacological approaches (e.g. biofeedback) with preventive medications improves outcomes
- Schedule follow-up visits to track outcome and modify treatment plans