

MIGRAINE MANAGEMENT

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To be discussed

- Definition of episodic vs. chronic migraine
- Updated evidence-based guidelines for the use of traditional and non-traditional agents for episodic migraine prevention
- Evidence to support the use of onabotulinumtoxinA (BOTOX) for the treatment of chronic migraine
- “New” migraine abortive agents on the horizon

Definitions

- Episodic vs. chronic migraine according to the International Classification of Headache Disorders (ICHD) criteria
- Important to be aware of diagnostic criteria for chronic migraine in particular when considering patients for BOTOX for treatment of chronic migraine

ICHD diagnostic criteria for (episodic) migraine

- A. At least 5 attacks fulfilling criteria B to D
- B. Headache attacks lasting 4 to 72 hours
- C. Headache has at least 2 of the following characteristics:
 1. Unilateral location
 2. Pulsating quality
 3. Moderate or severe pain intensity
 4. Aggravation by or causing avoidance of routine physical activity

ICHD diagnostic criteria for (episodic) migraine

- D. During headache at least one of the following:
 1. Nausea and/or vomiting
 2. Photophobia and phonophobia
- E. Not attributed to another disorder

ICHD diagnostic criteria for chronic migraine

- A. Headache on at least 15 days per month for at least 3 months
- B. Criteria for diagnosis of migraine are fulfilled
- C. On 8 days per month for at least 3 months the headache experienced either fulfills the criteria listed under C and D above or responds to treatment with a triptan or ergot
- D. Not attributed to another disorder

Prevention of episodic migraine

- Consider preventive approach to migraine in order to reduce the frequency and severity of migraine attacks
- Traditional agents act as vascular and neuronal stabilizers and include antihypertensive, antidepressant, and anticonvulsant drugs
- Non-traditional agents act as anti-inflammatories and vascular and neuronal stabilizers and include NSAIDs, vitamins, minerals, and herbal compounds

Traditional agents for migraine prevention

Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

Neurology 2012;78:1337-1345

Traditional agents for migraine prevention

Objective:

To provide updated evidence-based recommendations for the preventive treatment of migraine headache.

The clinical question addressed was: What pharmacologic therapies are proven effective for migraine prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?

Traditional agents for migraine prevention

Methods:

The authors analyzed published studies from June 1999 to May 2009 using a structured review process to classify the evidence relative to the efficacy of various medications available in the U.S. for migraine prevention.

The author panel reviewed 284 abstracts, which ultimately yielded 29 Class I or Class II articles on migraine prevention that were reviewed.

Traditional agents for migraine prevention

Results and Recommendations:

I. Medications that are established as effective and should be offered for migraine prevention include

- Divalproex sodium, sodium valproate, and topiramate
- Metoprolol, propranolol, and timolol
- Frovatriptan (for short-term prophylaxis of menstrually associated migraine only)

Traditional agents for migraine prevention

II. Medications that are probably effective and should be considered for migraine prevention include

- Amitriptyline and venlafaxine
- Atenolol and nadolol
- Naratriptan and zolmitriptan (for short-term prophylaxis of menstrually associated migraine only)

Traditional agents for migraine prevention

III. Medications that are possibly effective and may be considered for migraine prevention include

- Nebivolol and pindolol
- Lisinopril
- Candesartan
- Clonidine and guanfacine
- Carbamazepine

Non-traditional agents for migraine prevention

Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

Neurology 2012;78:1346-1353

Non-traditional agents for migraine prevention

Objective:

To provide updated evidence-based recommendations for the preventive treatment of migraine headache.

The clinical question addressed was: Are NSAIDs or other complementary treatments effective for migraine prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?

Non-traditional agents for migraine prevention

Methods:

The authors analyzed published studies from June 1999 to May 2009 using a structured review process to classify the evidence relative to the efficacy of various medications available in the U.S. for migraine prevention.

The author panel reviewed 284 abstracts, which ultimately yielded 49 Class I or Class II articles on migraine prevention; of these, 15 were classified as involving nontraditional therapies, NSAIDs, and other complementary therapies that were reviewed.

Non-traditional agents for migraine prevention

Results and Recommendations:

I. Petasites, a purified extract from the butterbur plant, is the only compound that was established as effective and should be offered for migraine prevention

- Petasites may demonstrate anti-inflammatory, antihistamine, and Ca channel blocking activity to produce an anti-migraine effect via blood vessel relaxation in particular

Non-traditional agents for migraine prevention

II. Compounds that are probably effective and should be considered for migraine prevention include

- Fenoprofen, ibuprofen, ketoprofen, naproxen, and naproxen sodium (anti-inflammatory effect)
- Riboflavin (?enhances mitochondrial function)
- Magnesium (neuronal stabilizing effect)
- Feverfew (?anti-inflammatory effect)
- Histamine SQ (old-fashioned histamine desensitization therapy)

Non-traditional agents for migraine prevention

III. Compounds that are possibly effective and may be considered for migraine prevention include

- Flurbiprofen and mefenamic acid (anti-inflammatory effect)
- Co-Q10 (?enhances mitochondrial function)
- Estrogen (vascular stabilizing effect)
- Cyproheptadine (antihistamine effect)

Chronic migraine

- A very small percentage of migraine sufferers develop chronic migraine
- Episodic migraine may transform into chronic migraine in the setting of hormonal changes, head trauma, or a major life stressor
- Chronic migraine may be fueled by medication and caffeine overuse, significant mood disorder, chronic pain issues, and comorbid medical conditions
- Chronic migraine is a very challenging disorder to treat

BOTOX for treatment of chronic migraine

- Unsuccessful exploratory studies for use of onabotulinumtoxinA (BOTOX) in treating chronic tension-type headache in particular led to its investigation for the treatment of chronic migraine
- BOTOX likely exerts its anti-migraine effect by blocking the release of neurotransmitters in the periphery thereby preventing peripheral signals from activating central pain pathways in the nervous system

BOTOX for treatment of chronic migraine

- BOTOX was approved for treatment of chronic migraine following the completion of the PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) clinical program in 2010
- BOTOX is now considered a potentially effective addition to our treatment strategy for chronic migraine

PREEMPT

Dodick D, Turkel C, DeGryse R, et al.

OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from double blinded, randomized, placebo-controlled phases of the PREEMPT clinical program.

Headache 2010;50(6):921-36.

PREEMPT

Objective:

To assess the efficacy, safety, and tolerability of onabotulinumtoxinA (BOTOX) as headache prophylaxis in adults with chronic migraine

Background:

Chronic migraine is a prevalent, disabling, and undertreated neurological disorder. Few preventive treatments have been investigated and none is specifically indicated for chronic migraine.

PREEMPT

Methods:

The 2 multicenter, pivotal trials in the PREEMPT: Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy clinical program each included a 24-week randomized, double-blind phase followed by a 32-week open-label phase.

Qualified patients were randomized to BOTOX (155-195 U) or placebo injections every 12 weeks. Study visits occurred every 4 weeks.

PREEMPT

These studies were identical in design, with the only exception being the designation of the primary and secondary endpoints.

The primary endpoint for the pooled analysis was mean change from baseline in frequency of headache days at 24 weeks.

PREEMPT

Secondary endpoints included mean change from baseline to week 24 in

- frequency of migraine days/episodes
- total cumulative hours of headache on headache days
- frequency of acute headache pain medication intakes
- the proportion of patients with severe Headache Impact Test-6 score at week 24.

PREEMPT

Results:

A total of 1384 adults were randomized to BOTOX (n=688) or placebo (n=696).

Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring BOTOX over placebo at week 24 and at all other time points.

PREEMPT

Significant differences favoring BOTOX were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes.

Adverse events occurred in 62.4% of BOTOX patients and 51.7% of placebo patients. Most patients reported adverse events that were mild to moderate in severity and few discontinued due to adverse events. No unexpected treatment-related adverse events were identified.

PREEMPT

Conclusions:

The pooled PREEMPT results demonstrate that BOTOX is an effective prophylactic treatment for chronic migraine.

BOTOX resulted in significant improvements compared with placebo in multiple headache symptom measures, and significantly reduced headache-related disability and improved functioning, vitality, and overall health-related quality of life. Repeat treatments with BOTOX were safe and well tolerated.

On the horizon

- For years, triptans have been the mainstay of acute migraine abortive therapy
- Triptans act on a specific serotonin receptor in the brainstem in order to prevent the activation of central pain pathways in the nervous system
- Other agents that may be useful for acute migraine abortive therapy include long-acting NSAIDs, anti-emetics, tranquilizers, and dihydroergotamine (DHE)
- No new classes of drugs are expected to be available in the near future for migraine treatment

On the horizon

- However, new formulations of already-existing migraine abortive therapies have been developed and should be available in the near future in the U.S.
- These include sumatriptan, zolmitriptan, and dihydroergotamine (DHE)
- The objective is to improve the delivery of these medications and reduce side effects

On the horizon

Sumatriptan is currently available for delivery in a SQ injectable preparation (with and without a needle), nasal spray, and oral tablet

- OptiNose will utilize a bi-directional, breath-actuated device in order to deliver a fine powder of sumatriptan into the nasal cavity
- Zecuity will utilize a small electric current to drive sumatriptan across the skin via an iontophoretic transdermal patch

On the horizon

Zolmitriptan is currently available for delivery in a nasal spray, oral tablet, and orally-disintegrating tablet

- Zolmitriptan Rapidfilm is a polymeric film strip that will deliver zolmitriptan by dissolving on the tongue (already available in Europe)

On the horizon

Dihydroergotamine (DHE) is currently available for delivery in a nasal spray, IV infusion, and IM and SQ injection (not assembled)

- Levadex is an oral inhaler that will deliver DHE to the lung automatically after breath actuation; Levadex is reported to provide similar onset of action and efficacy comparable to IV DHE

In conclusion

- Consider the updated evidence-based guidelines when choosing traditional and non-traditional agents for migraine prevention
- Consider onabotulinumtoxinA (BOTOX) for treatment of patients who meet the diagnostic criteria for chronic migraine
- Consider the use of new preparations and delivery systems of sumatriptan, zolmitriptan, and dihydroergotamine (DHE) for migraine abortive therapy once they are available in the U.S.
- Consider referral to a neurologist for help!

Summary of references

1. Dodick D, Turkel C, DeGryse R, et.al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010 Jun;50(6):921-36.
2. Holland S, Silberstein S, Freitag F, et.al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78;1346-53.
3. Nagy A and Rapoport A. Update on future headache treatments. *Neurological Sciences* 2013 May;34 Suppl 1;S101-8.
4. Silberstein S, Holland S, Freitag F, et.al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78;1337-45.