MANAGEMENT OF MIGRAINE

Management of Migraine

Acute Strategies
To interrupt attacks

Preventative Strategies
To prevent attack recurrence

Pre-emptive Strategies
Used when a known headache trigger exists

Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57; American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Goals of Management of Migraine

Goals of Acute Treatment for Migraine

- Treat attacks quickly and consistently and avoid recurrence
- Restore patient function in personal, social, and work domains
- Minimize the use of backup and rescue medications
- Eliminate or minimize adverse events
- Optimize self-care and reduce the need for resource use
- Provide cost-effective care

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

U.S. Headache Consortium – Goals for Migraine Treatment

Goals for Successful Treatment of Acute Migraine Attacks	Goals of Long-term Migraine Management
• Treat migraine attacks rapidly and consistently without recurrence • Restore patient's ability to function • Minimize use of back-up and rescue medications • Optimize self-care for overall management • Cause minimal or no adverse effects	• Reduce migraine frequency and severity • Reduce disability • Improve quality of life • Prevent headache • Avoid escalation of headache medication use • Educate and enable patients to manage their disease

Matchar DB et al. Available at: http://tools.aan.com/professionals/practice/pdfs/gl0087.pdf. Accessed 27 November, 2014.

Trigger Identification and Avoidance

Evaluating Migraine Triggers

- A trigger causes headache within 24 h >50% of the time
- Do not confuse triggers with the cause of headache
- Not all triggers act equally to provoke headache
- There may be a “load” factor
- The presence of multiple triggers or a combination of particular triggers may be needed to provoke headache

Patients should be advised to avoid known triggers if possible and counselled on lifestyle and stress management

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

Common Migraine Triggers

DIET
Hunger
Alcohol
Additives
Red wine
Artificial sweeteners
Monosodium glutamate
Citrus fruits
Foods containing tyramine (*e.g.*, aged cheese)
Meats with nitrites
Caffeine/caffeine withdrawal

ENVIRONMENTAL
Light glare/visual stimuli
Odors
Altitude
Weather change
Smoking
Motion sickness
Cold stimulus (*e.g.*, ice cream headache)

HORMONAL
Menstruation
Menopause
Pregnancy

STRESS AND ANXIETY

HEAD OR NECK PAIN
Trauma
Other causes

CHRONOBIOLOGIC
Sleep (too little/too much)
Schedule change

MEDICATIONS
Vasodilators
Oral contraceptives

PHYSICAL EXERTION
Exercise
Sex

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014; Chawla J. 2014. Available at http://emedicine.medscape.com/article/1142556-overview. Accessed 05 January 2014.

Individualized Management Strategies

Considerations when Planning Acute Treatment in Migraine

- Patient age
- Current health status
- Coexistent illnesses
- Migraine type

It is important to use a patient-centered approach when planning acute treatment in migraine

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

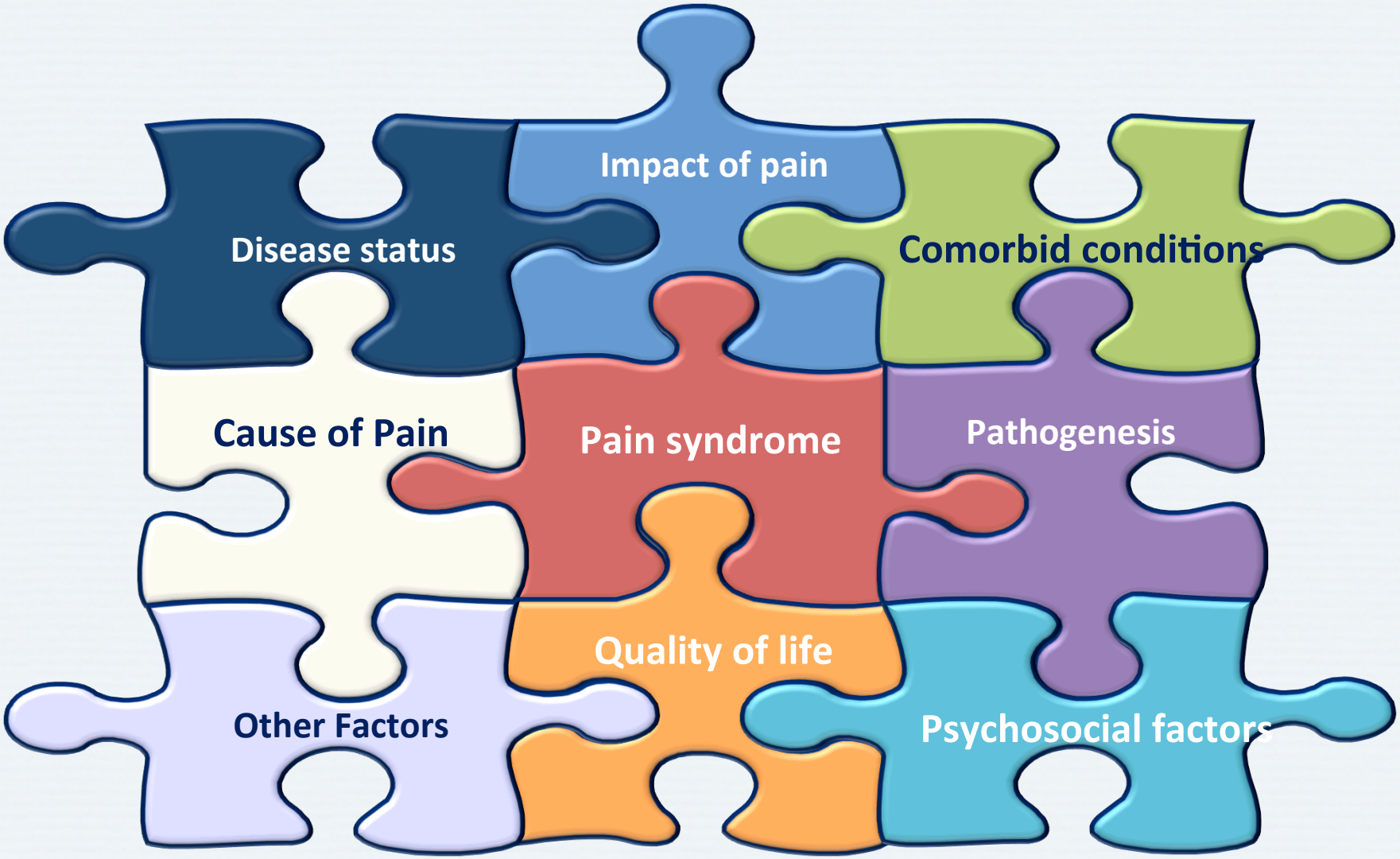
Considerations when Selecting a Medication for Acute Treatment of Migraine

- Frequency of headaches
- Severity of headaches
- How quickly the headache builds
- Duration of the headache
- Tendency for headache recurrences
- Disability caused by headaches
  - As disability increases, non-specific treatments are less liable to work
- Associated symptoms (*e.g.*, nausea)
- Previous response to therapy
- Adverse events associated with medications
- Patient preference

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Selecting appropriate treatment for each patient (individualization of treatment after diagnosis and assessment of impact of migraine by considering all treatment modalities, including non-pharmacological)

Many Factors Must Be Considered when Treating a Patient with Migraine



Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Overview of Treatment of Migraine

Overview of Acute Pain Management in Patients with Migraine

Type of Migraine	Suggested Medications
Mild to moderate attacks or severe attacks that have responded to similar agents in the past	• NSAIDs (oral) • Combination analgesics with caffeine • Isometheptene combinations
Moderate to severe or mild to moderate attacks that respond poorly to NSAIDs	• Migraine-specific drugs (e.g., triptans, DHE) **Or** • Combination therapy (e.g., ASA + acetaminophen + caffeine) **Or** • Other drugs (e.g., ergotamine)
Severe attacks that do not respond to other treatments	• Self-administered rescue medication

- **Limit and carefully monitor the use of opiates and butalbital analgesics**
- **Migraine accompanied by nausea or vomiting: use a non-oral route of administration**

ASA = acetylsalicylic acid; DHE = dihydroergotamine

Aukerman G *et al. Am Fam Physician.* 2002;66(11):2123-30.

Non-pharmacological Management of Migraine

Multimodal Pain Management

CBT = cognitive behavioral therapy

Patients Who Will Benefit from Non-drug Therapies for Migraine

- Poor tolerance for specific medications
- Contraindications to specific medications
- Insufficient or no response to medications
- Pregnant/nursing women or those who are planning pregnancy
- History of long-term, frequent, or excessive use of acute medications that have aggravated their headaches
- Significant stress

TENS = transcutaneous electrical nerve stimulation

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

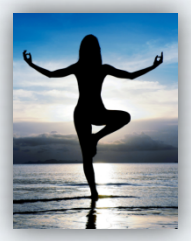
Non-pharmacologic Therapy for Migraine

Therapy	Comments
Massage Spinal manipulation Hyperbaric oxygen Percutaneous estradiol	• Varying degrees of efficacy
Herbal supplements Dietary supplements	• Range from effective to unclear efficacy
Yoga	• Reduces migraine frequency and associated clinical features
Acupuncture	• Conflicting data • One study showed acupuncture was more effective than topiramate in chronic migraine prophylaxis
Surgery	• Surgical manipulation of ≥1 migraine trigger site can successfully eliminate or reduce the frequency, duration, and intensity of migraine headache in a lasting manner

Holland S *et al. Neurology.* 2012;78(17):1346-53; Lester M. 2012. Available at: http://nccam.nih.gov/sites/nccam.nih.gov/files/D462.pdf. Accessed 14 December, 2014; John PJ *et al. Headache.* 2007;47(5):654-61; Mauskop A. *Continuum (Minneap Minn).* 2012;18(4):796-806; Linde K *et al. JAMA*. 2005;293(17):2118-25; Yang CP *et al. Cephalalgia.* 2011;31(15):1510-21; Guyuron B*et al. Plast Reconstr Surg.* 2009;124(2):461-8; Guyuron B *et al. Plast Reconstr Surg.* 2011;127(2):603-8.

Complementary Health Approaches for Migraine Prevention

- Mind and body interventions
  - Relaxation training
  - Biofeedback
  - Acupuncture*
  - Tai Chi
  - Yoga
  - Cognitive Behavioral Therapy
  - Aerobic exercise
- Massage
- Spinal manipulation
- Hyperbaric oxygen
- Percutaneous estradiol†
- Dietary supplements



Therapies vary in efficacy in treating migraine

*Conflicting data exist

†Increased risk of migraine after discontinuation of estradiol

Holland S *et al. Neurology.* 2012;78(17):1346-53; Lester M. 2012. Available at: http://nccam.nih.gov/sites/nccam.nih.gov/files/D462.pdf. Accessed 14 December, 2014; John PJ *et al. Headache.* 2007;47(5):654-61; Mauskop A. *Continuum (Minneap Minn).* 2012;18(4):796-806.

Complementary Health Approaches for Migraine

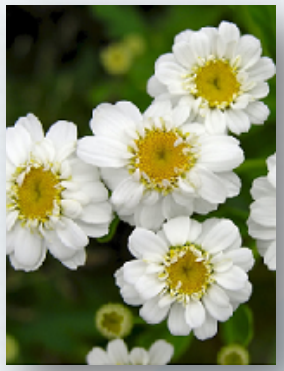
- Some alternative therapies may be helpful
- Often have a very low risk of serious side effects
- Many are less costly than pharmacologic therapies
- Considering the combination of efficacy, minimal side effects, and cost savings, it may be helpful to prescribe medications in combination with non-pharmacologic therapies

Do not replace proven conventional medical treatments for migraine with unproven products or practices.

Mauskop A. *Continuum (Minneap Minn).* 2012;18(4):796-806.

Herbal Preparations, Dietary Supplements and Other Interventions for Migraine Prevention

Preparation	Efficacy
Butterbur	Effective
Feverfew	Probably effective
Magnesium	
Riboflavin	
Coenzyme Q10	
Estrogen*	
Omega-3 fatty acids	Efficacy unclear
Hyperbaric oxygen	



*Increased risk of migraine after discontinuation of estradiol

Holland S *et al. Neurology.* 2012;78(17):1346-53; Lester M. 2012. Available at: http://nccam.nih.gov/sites/nccam.nih.gov/files/D462.pdf. Accessed 14 December, 2014; John PJ *et al. Headache.* 2007;47(5):654-61.

Yoga for Migraine

- Patients with migraine without aura were taught yoga
- Yoga group was taught techniques to practice at prodromal stage of migraine, whenever possible
  - 60 minutes 5 days/week for 3 months
  - Included:
    - Yoga postures
    - Breathing practices
    - Relaxation practices and meditation
- Yoga group patients were not to practice during headache, resolution, and postdrome stage

John PJ *et al. Headache.* 2007;47(5):654-61.

Yoga for Migraine

Variable	Yoga Group	Self-Care Group	*P* Value
Frequency	4.56 ± 1.79	10.18 ± 2.14	.001
Most pain	4.91 ± 0.89	8.24 ± 0.71	.001
Lowest pain	2.53 ± 0.72	3.77 ± 0.89	.001
Average pain	4.64 ± 0.72	7.81 ± 0.87	.001
Duration of attack	4.78 ± 1.01	6.42 ± 1.27	.001
Medication score	1.37 ± 1.01	3.94 ± 0.97	.001
McGill pain questionnaire			
S-PRI	1.62 ± 0.49	2.91 ± 0.29	.001
A-PRI	1.56 ± 0.50	2.64 ± 0.49	.001
T-PRI	3.19 ± 0.69	5.54 ± 0.50	.001
Overall intensity	1.69 ± 0.47	3.97 ± 0.58	.001
HADS			
Anxiety score	4.69 ± 1.42	13.39 ± 1.73	.001
Depression score	4.34 ± 1.33	13.21 ± 1.92	.001

Yoga significantly reduced migraine frequency and associated clinical features when practised for 3 months by migraine sufferers

HADS = hospital anxiety depression scale; S-PRI = sensory pain rating index; A-PRI = affective pain rating index; T-PRI = total pain rating index; evaluative overall intensity of total pain experience; pain-visual analog scale

John PJ *et al. Headache.* 2007;47(5):654-61.

Surgical Treatment for Migraine

- 75 patients underwent surgery (n=49) or sham surgery (n=26)
  - Three trigger sites identified: frontal, temporal, occipital
- More patients (83.7%) in actual surgery group experienced ≥50% reduction in migraine than sham surgery patients (57.7%) ($p<0.05$)
- More patients (57.1%) in actual surgery group reported complete elimination of migraine (vs. 3.8% in sham surgery group; $p<0.001$)
- Compared with control group, actual surgery group demonstrated significant improvements in all validated migraine measurements at one year
  - Improvements were not dependent on trigger site
- Most common surgical complication: slight hollowing of temple in group with temporal migraine

Surgical deactivation of peripheral migraine trigger sites is an effective alternative for patients who suffer from frequent moderate to severe migraines that are difficult to manage using standard protocols.

Guyuron B*et al. Plast Reconstr Surg.* 2009;124(2):461-8; Guyuron B *et al. Plast Reconstr Surg.* 2011;127(2):603-8.

Surgical Treatment for Migraine – Results at 5 Years

Baseline, 1- and 5-Year Follow-Up, and Mean Change from Baseline at 5 Years after Surgery

Variable	Baseline	1 Year	5 Years	Mean Change (Baseline to 5 Years)	p*
Frequency, MH/month	10.9 ± 7.46	4.0 ± 6.39	4.0 ± 5.34	6.9 ± 7.57	<0.0001
Intensity (analog scale 0–10)	8.5 ± 1.23	4.0 ± 3.27	4.5 ± 3.18	4.0 ± 3.18	<0.0001
Duration (days)	1.4 ± 1.40	0.42 ± 0.76	0.31 ± 0.87	1.04 ± 1.21	<0.0001
MH index (*frequency* × *intensity* × *duration*)	90.3 ± 80.10	10.5 ± 16.66	11.4 ± 29.92	78.9 ± 76.42	<0.0001
MIDAS	3.6 ± 0.72	1.8 ± 1.37	1.7 ± 1.55	1.9 ± 1.56	<0.0001
MSQEM (Mental Migraine Score)	47.0 ± 24.72	83.3 ± 23.61	82.0 ± 26.39	34.9 ± 29.52	<0.0001
MSQPRE	65.7 ± 20.06	88.1 ± 15.98	86.4 ± 20.13	20.7 ± 21.53	<0.0001
MSQRES	45.1 ± 18.21	79.6 ± 21.81	78.7 ± 22.03	33.5 ± 25.37	<0.0001
SFMEN	43.2 ± 11.09	47.8 ± 9.00	48.4 ± 10.56	5.2 ± 5.34	<0.0001
SFPH	43.7 ± 9.66	51.1 ± 9.15	47.7 ± 9.87	4.0 ± 5.34	<0.0001

MH, migraine headache; MIDAS, Migraine Disability Assessment; MSQEM, Migraine-Specific Questionnaire; MSQPRE, Migraine-Specific Questionnaire, Preventive; MSQRES, Migraine-Specific Questionnaire, Restrictive; SFMEN, Medical Outcomes Study 36-Item Short Form Health Survey, Mental; SFPH, Medical Outcomes Study 36-Item Short Form Health Survey, Physical.
All values are mean ± SD.
*The p values were obtained from paired t test and confirmed by Wilcoxon signed rank test.

Based on 5-year follow-up data, strong evidence suggests surgical manipulation of ≥1 migraine trigger site can successfully eliminate or reduce the frequency, duration, and intensity of migraine headache in a lasting manner

Guyuron B*et al. Plast Reconstr Surg.* 2009;124(2):461-8; Guyuron B *et al. Plast Reconstr Surg.* 2011;127(2):603-8.

Neuromodulation for Migraine

- Possible treatments for chronic migraine
  - Occipital nerve stimulation
  - Supraorbital neurostimulation
  - Single-pulse transcranial magnetic stimulation
  - Vagal nerve stimulation
  - Sphenopalatine ganglion stimulation
  - Transcranial magnetic stimulation
- Attention is now on non-invasive neurostimulation devices
- Nerve stimulation may produce paresthesias or pain

Tso AR, Goadsby PJ. *Curr Treat Options Neurol.* 2014;16:318.

Pharmacologic Management of Migraine – Acute Treatment

Principles for Acute Treatment of Migraine

- Enlist patient in a therapeutic alliance
- Treat headache as early in attack as possible
- Tailor treatment to both individual and specific attack
- Headaches vary across individuals and attacks
- Limit medication use to two to three times/week
- Use correct dose and give full therapeutic trial
- Match drug formulation to symptom profile
- Suggest behavioral strategies to minimize headache frequency and impact
- Consider addition of preventative therapy
- Provide acute therapy for patients receiving preventative therapy

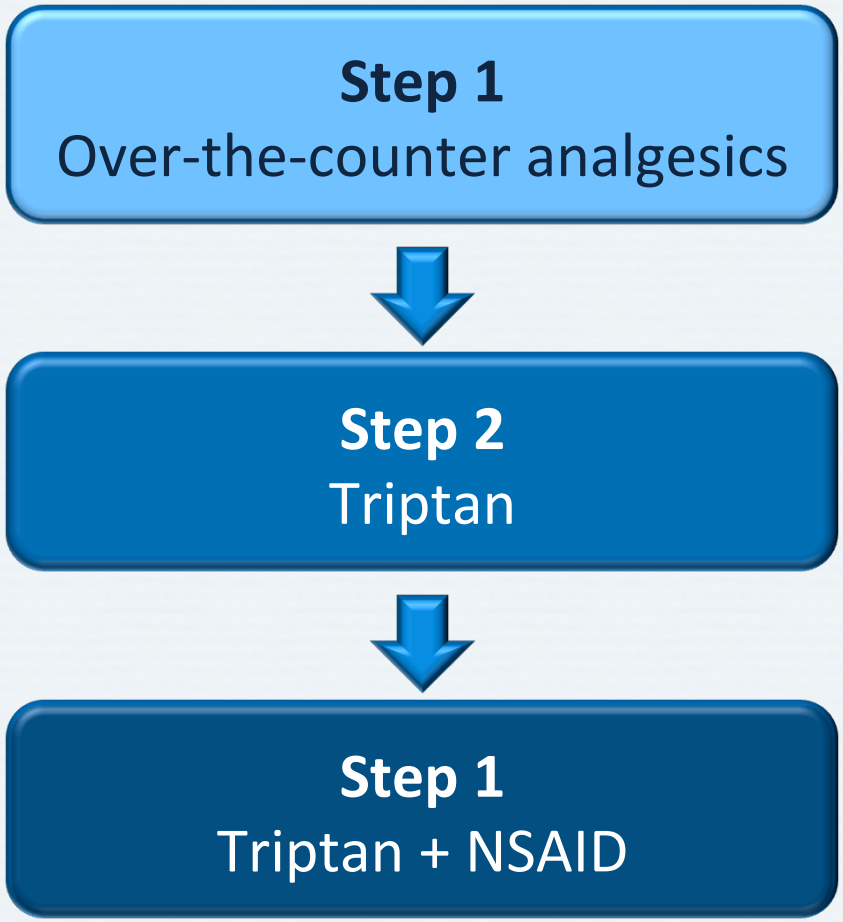
American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Acute Treatment in Migraine

- May be sufficient for patients who suffer infrequent attacks
- Must consider patient preference and contraindications
- Drug should be taken as soon as headache component of attack is realized
- Drug dose should be high enough to be fully effective
- Co-administration of anti-emetic or pro-kinetic drugs may help with absorption of primary drug and increase its speed of action and efficacy
- Overuse of any acute anti-migraine drug may induce chronification and medication overuse headache
- Severity and response to treatment vary between attacks
- Patients may need prescriptions for several drugs of increasing potency to manage their attacks to allow for a combined stratified and step-wise medication strategy

Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57.

Stepwise Approach to Treatment of Acute Migraine



An anti-emetic can be added at any step

NSAID = non-steroidal antiinflammatory drug

Best Pract J. 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Pharmacological Treatment of Migraine (1)

Drug(s)	Comments
Acetaminophen	• Limited data to support use as monotherapy in migraine
ASA	• Monotherapy may benefit some patients • Doses required may not be tolerated by some patients • Significant risk of GI adverse events
ASA + acetaminophen + caffeine	• Caffeine enhances absorption and may potentiate activity • Role of combination in moderate to severe migraine not supported by clinical trials • Increased potential for MOH • ASA side effects + caffeine side effects (insomnia, restlessness, palpitations)
NSAIDs/coxibs	• Effective for mild to severe migraine • Improves pain free periods and decreases pain and migraine-associated symptoms • Significant risk of GI adverse events

ASA = acetylsalicylic acid; coxib = cyclooxygenase inhibitor; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug

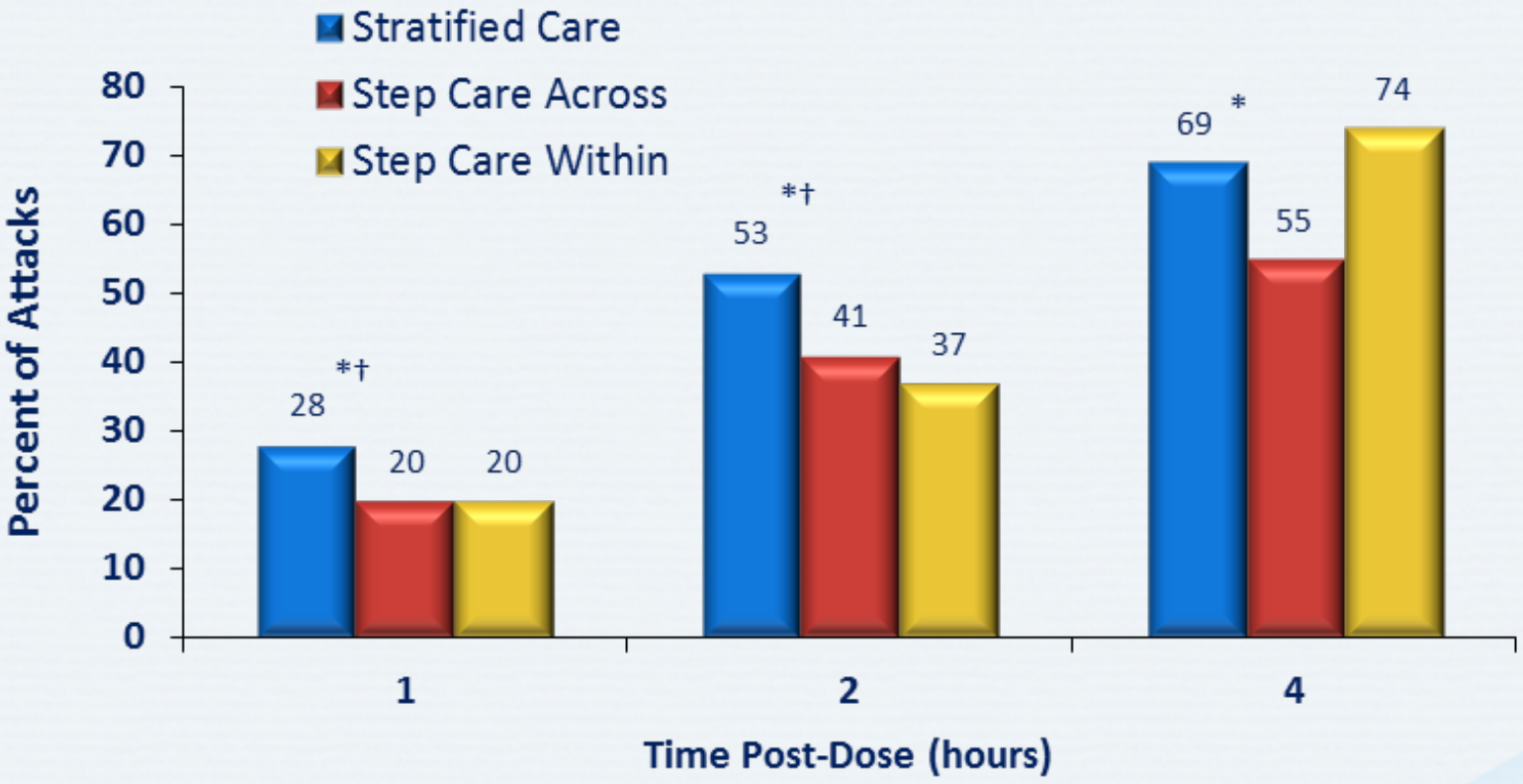
Demaagd G. *P T.* 2008;33(7):404-16; Aukerman G *et al. Am Fam Physician.* 2002;66(11):2123-30.

Pharmacological Treatment of Migraine (2)

Drug(s)	Comments
Barbiturates (especially butalbital)	• Used for many years but no data support use • Associated with a variety of adverse events • Patients regularly using barbiturates be evaluated and provided with an alternative therapy
Opioids	• Use should be limited in treatment of migraine • Short-term use may be appropriate in some patients • Use must be vigilantly monitored
Triptans	• Rapid onset of action • High efficacy • Favourable side effect profile
Ergot alkaloids	• Long history of use and low cost, but many possible associated adverse events • Largely been replaced by triptans Complex pharmacology and potential drug interactions (notably triptans) • Erratic pharmacokinetics

Demaagd G. *P T.* 2008;33(7):404-16; Silberstein SD. *Neurology.* 2000;55(6):754-762; Silberstein SD *et al*. Headache in Clinical Practice. Oxford, England: Isis Medical Media; 1998; Goadsby PJ *et al. N Engl J Med.* 2002;346(4):257-70.

Stratified Care for Migraine



Stratified vs. Step Care Across Attacks and Within Attacks ≤6 Attacks

P<0.001 for stratified care vs. step care across attacks (*) and for stratified care vs. step care within attacks (†)
Lipton RB *et al. JAMA*. 2000;284(20):2599-605.

Acute Treatment: Mechanism-based Management of Migraine

Simple Analgesics for the Acute Treatment of Migraine

- Three general classes
  - Acetaminophen
  - Acetylsalicylic acid (ASA) (alone or in combination)
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

Demaagd G. *P T.* 2008;33(7):404-16.

Acetaminophen for Acute Treatment of Migraine

- Limited data support use of acetaminophen as monotherapy in acute management of migraine
- One placebo-controlled trial reported benefits with 1,000 mg in mild-to-moderate migraine
  - Comparison trials with NSAIDs reported greater efficacy with NSAIDs

Acetaminophen's **mechanism of action** is probably achieved through a central mechanism related to **prostaglandin inhibition**

NSAID = non-steroidal anti-inflammatory drug

Demaagd G. *P T.* 2008;33(7):404-16.

Acetaminophen

- Action at molecular level is unclear
- Potential mechanisms include:
  - Inhibition of COX enzymes (COX-2 and/or COX-3)
  - Interaction with opioid pathway
  - Activation of serotoninergic bulbospinal pathway
  - Involvement of nitric oxide pathway
  - Increase in cannabinoid-vanilloid tone

COX = cyclooxygenase

Mattia A, Coluzzi F. *Minerva Anestesiol* 2009; 75(11):644-53.

ASA for the Acute Treatment of Migraine

- Monotherapy may benefit some patients
- Required doses are not always tolerated by patients with gastrointestinal symptoms
- May be benefits vs. placebo with 900-1000 mg in mild to severe migraine
- **Mechanism of action** probably similar to that of other NSAIDs that act on anti-inflammatory response in migraine
- Possible associated **adverse events**
  - Gastrointestinal upset
  - Suppositories may cause rectal irritation

ASA should probably be reserved as a second-line or third-line option

ASA = acetylsalicylic acid

Demaagd G. *P T.* 2008;33(7):404-16; Aukerman G *et al. Am Fam Physician.* 2002;66(11):2123-30.

ASA + Acetaminophen + Caffeine for the Acute Treatment of Migraine

- Caffeine enhances absorption and may potentiate activity
- May relieve headache intensity and migraine-associated symptoms (nausea, vomiting) in patients with mild to moderate migraine
  - Similar or greater efficacy with combination vs. other simple analgesics
- Possible **adverse events**
  - Increased potential for medication overuse headache
  - Caffeine can lead to insomnia, restlessness, and palpitations

Role of this combination in moderate to severe migraine has not been demonstrated in clinical trials

ASA = acetylsalicylic acid

Demaagd G. *P T.* 2008;33(7):404-16.

NSAIDs/Coxibs for the Acute Treatment of Migraine

- Effective in abortive therapy of mild to severe migraine
  - Improvement in pain-free periods, reductions in pain intensity and migraine-associated symptoms
- Combination with caffeine or other abortive agents – including triptans – may offer additional benefit in some patients
- Proposed **mechanism of action** is via anti-inflammatory effects on vasoactive peptide-induced inflammation that may occur during migraine
- Possible **adverse events**
  - Gastrointestinal
  - Addition of metoclopramide may improve tolerability

NSAIDs may be appropriate as acute migraine therapy in patients with infrequent, mild to severe attacks who experience minimal GI symptoms

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug

Demaagd G. *P T.* 2008;33(7):404-16.

What Are NSAIDs (nsNSAIDs/coxibs)?

NSAID = **N**on-**S**teroidal **A**nti-**I**nflammatory **D**rug

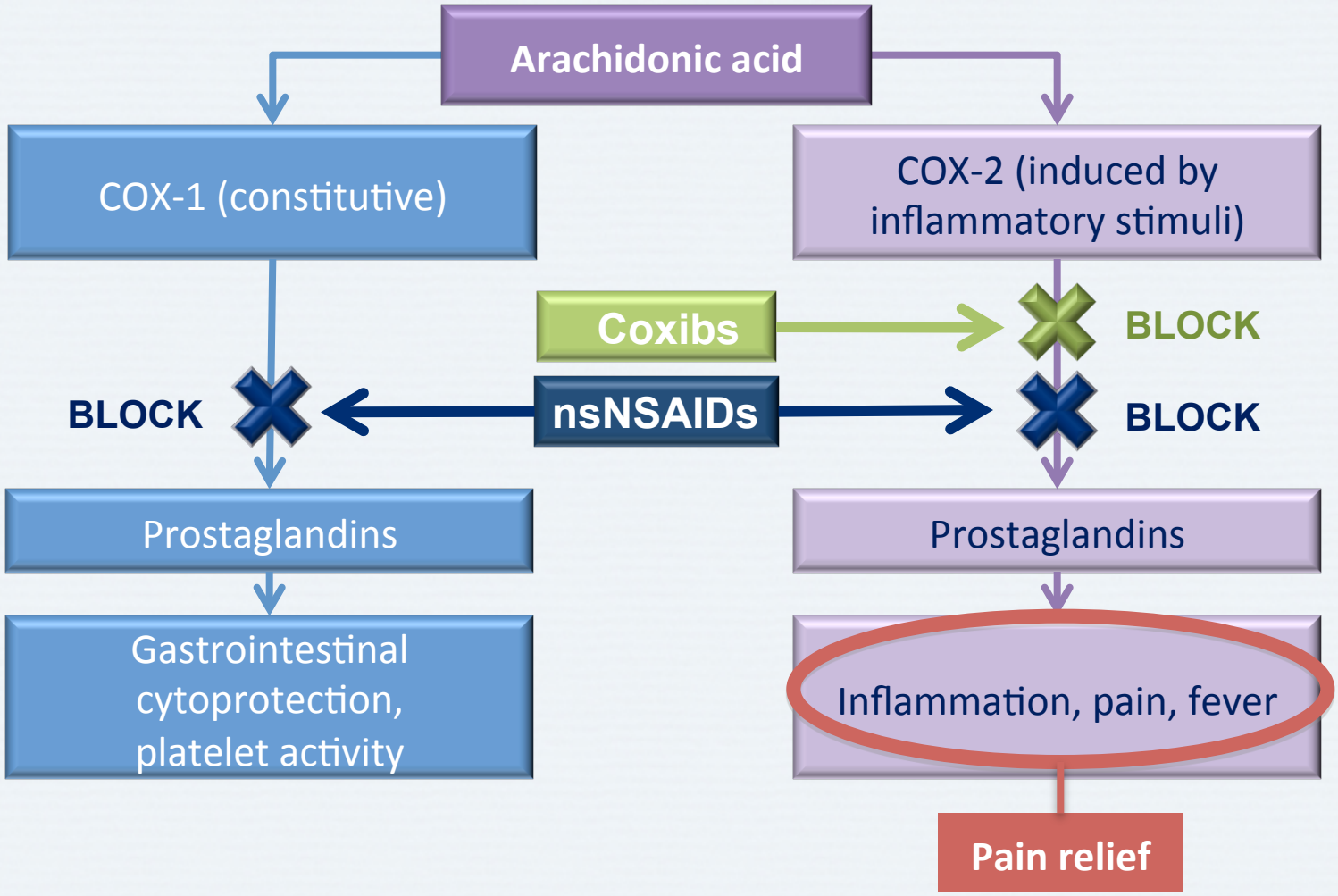
- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications:

nsNSAIDs:	*Coxibs:*
– ASA	– Celecoxib
– Diclofenac	– Etoricoxib
– Ibuprofen	
– Naproxen	

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Brune K. In: Kopf A *et al* (eds).. *Guide to Pain Management in Low-Resource Settings* International Association for the Study of Pain; Seattle, WA: 2010.

How Do nsNSAIDs/Coxibs Work?



Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID

Gastrosource. *Non-steroidal Anti-inflammatory Drug (NSAID)-Associated Upper Gastrointestinal Side-Effects*. Available at: http://www.gastrosource.com/11674565?itemId=11674565. Accessed: December 4, 2010; Vane JR, Botting RM. *Inflamm Res* 1995;44(1):1-10.

Adverse Effects of nsNSAIDs/Coxibs

All NSAIDs

- Gastroenteropathy - gastritis, bleeding, ulceration, perforation
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Allergic phenomenon

Cox-1-mediated NSAIDs (nsNSAIDs)

- Decreased platelet aggregation

Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID

Clemett D, Goa KL. *Drugs* 2000; 59(4):957-80; Grosser T *et al.* In: Brunton L *et al* (eds.). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

Barbiturates for Acute Treatment of Migraine

- Combination products used for many years for migraine
  - No data support use of butalbital
- Available in combination with acetaminophen or ASA (± codeine)
- Possible **adverse events**
  - Central nervous system depression and confusion
  - Negative effects on cognition
  - May case paradoxical excitation
  - Medication overuse headache
- Can lead to abuse and dependency

Although butalbital is considered an abortive therapy in migraine, patients regularly using barbiturates should be evaluated and provided with an alternative therapy

ASA = acetylsalicylic acid

Demaagd G. *P T.* 2008;33(7):404-16.

Opioid Analgesics for the Acute Treatment of Migraine

- Limit/avoid use due to potential for:
  - Overuse
  - Abuse
  - Tolerance
  - Risk of medication overuse headache
  - Possibility of opioid-induced hyperalgesia in some patients
- **Short-term** use may be appropriate in some patients:
  - Women with intractable menstrual migraine
  - Pregnant women
  - The elderly
  - Patients with severe and debilitating head pain who are intolerant of or unresponsive to other medications

Use of opioid analgesics should be vigilantly monitored by patients, their family members, and their health care professionals

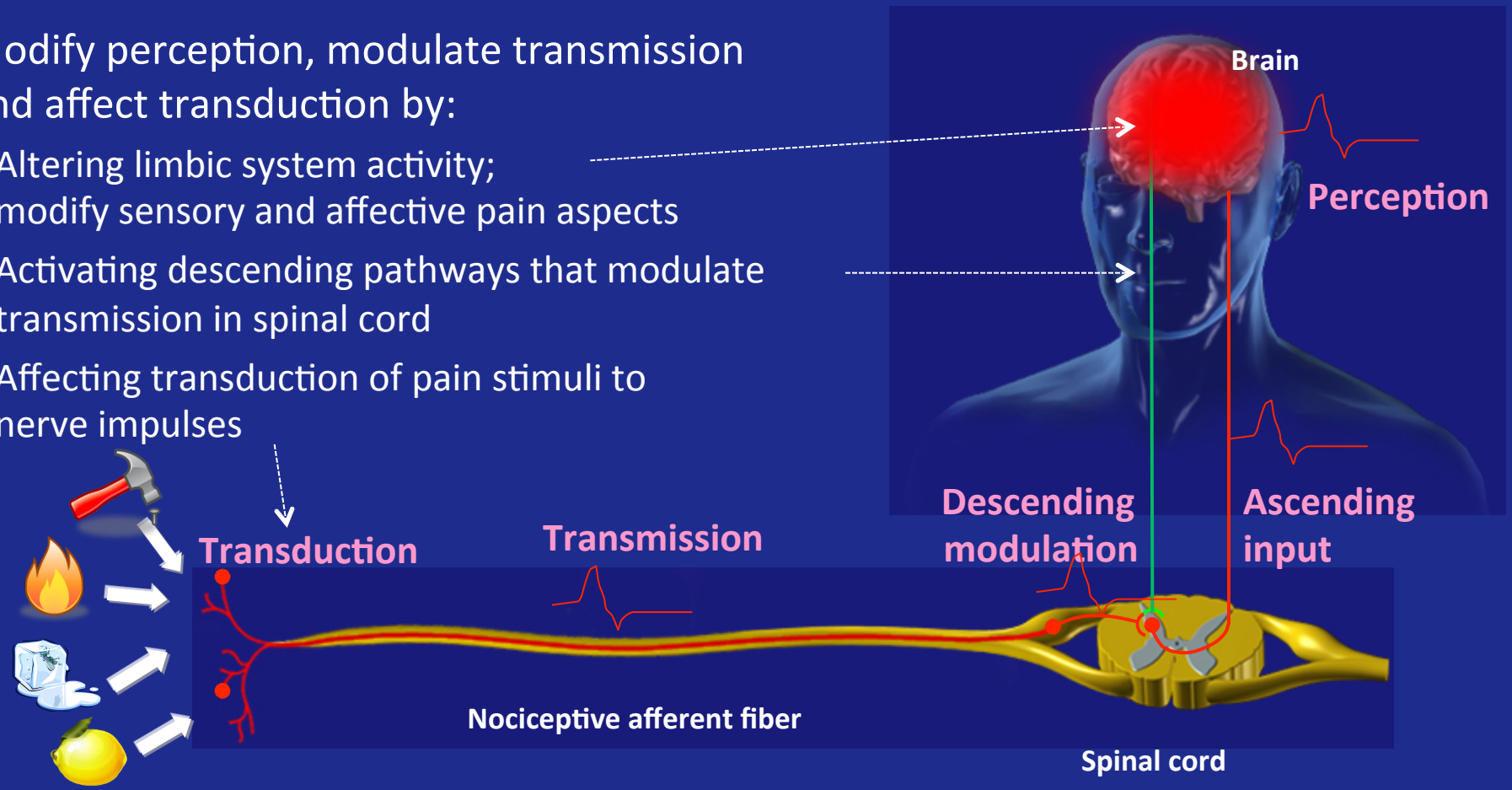
ASA = acetylsalicylic acid

Demaagd G. *P T.* 2008;33(7):404-16.

How Opioids Affect Pain

Modify perception, modulate transmission and affect transduction by:

- Altering limbic system activity; modify sensory and affective pain aspects
- Activating descending pathways that modulate transmission in spinal cord
- Affecting transduction of pain stimuli to nerve impulses



Reisine T, Pasternak G. In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7; Trescot AM *et al. Pain Physician* 2008; 11(2 Suppl):S133-53.

Adverse Effects of Opioids

System	Adverse effects
Gastrointestinal	Nausea, vomiting, constipation
CNS	Cognitive impairment, sedation, lightheadedness, dizziness
Respiratory	Respiratory depression
Cardiovascular	Orthostatic hypotension, fainting
Other	Urticaria, miosis, sweating, urinary retention

CNS = central nervous system

Moreland LW, St Clair EW. *Rheum Dis Clin North Am* 1999; 25(1):153-91; Yaksh TL, Wallace MS. In*:* Brunton L *et al* (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

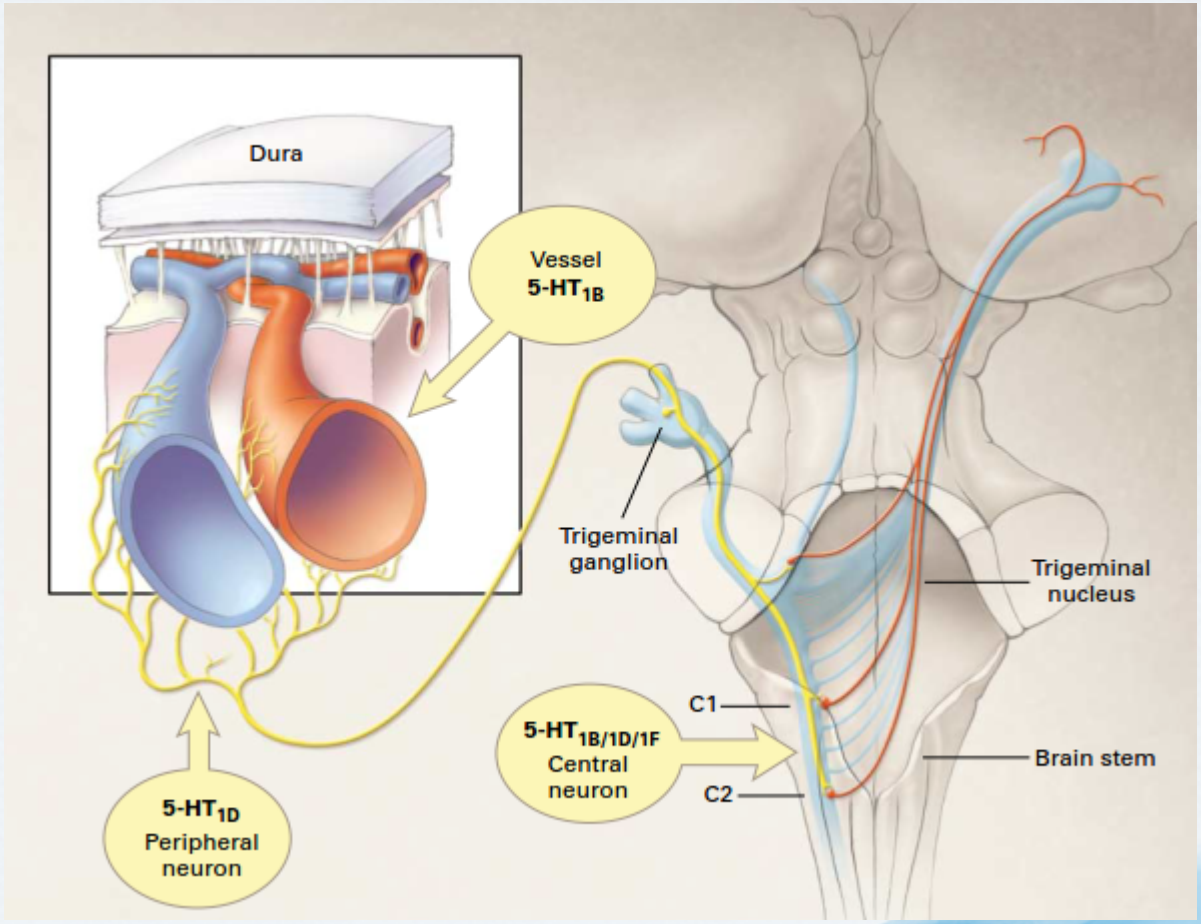
Triptans for Acute Treatment of Migraine

- Selective 5-$HT_{1B/1D/1F}$ agonists
- Rapid onset of action (15 to 60 min)
- High efficacy
- Favourable side effect profile

Silberstein SD. *Neurology.* 2000;55(6):754-762; Silberstein SD *et al*. Headache in Clinical Practice. Oxford, England: Isis Medical Media; 1998.

How Do Triptans Work to Relieve Migraine?

Possible Sites of Action of Triptans in the Trigeminovascular System



Goadsby PJ *et al. N Engl J Med.* 2002;346(4):257-70.

Triptans: Treatment Choices

Sumatriptan
- Tablet and fast-disintegrating
- Injection
- Nasal spray

Zolmitriptan
- Tablet and melt
- Nasal spray

Naratriptan
- Tablet

Rizatriptan
- Tablet and melt

Almotriptan
- Tablet

Frovitriptan
- Tablet

Eletriptan
- Tablet

Ferrari MD *et al. Lancet*. 2001;358(9294):1668-75; Worldwide Product Safety and Pharmacovigilance Document. December 1999.

Choosing a Triptan

- All triptans have similar efficacy
  - Base choice on patient preference
- Patients often prefer oral therapy
  - Vomiting and nausea may preclude use of oral treatment →consider subcutaneous or nasal formulations
- Patients who do not respond to one triptan may respond to a different one
  - Try an alternative triptan in a subsequent attack
- Patients who do not respond to oral triptans should be encouraged to try subcutaneous formulations

Best Pract J. 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Prescribing Triptans and Monitoring Use

- Most effective if taken early in a migraine attack
- Do not take during aura phase
- Dose should not be repeated if there is no response
  - Dose can be repeated after two to four hours if there was initial relief from the migraine and it has reoccurred
- Avoid using triptans for ≥10 days/month

A triptan should be taken early during a migraine attack

A triptan should not be taken during the aura phase

In absence of a response, the dose of triptan should not be repeated

Best Pract J. 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Triptans: Contraindications

- Pregnancy
- Lactation
- Ischemic stroke
- Ischemic heart disease
- Prinzmetal's angina
- Raynaud's disease

- Uncontrolled hypertension
- Severe liver or renal failure
- Familial hemiplegic migraine
- Basilar migraine
- Ergotamine therapy
- MAOI therapy

MAO = monoamine oxidase

Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4(1):70-81.

Triptans: Drug-drug Interactions

- Contraindicated in patients either currently taking MAOIs or within two weeks of stopping an MAOI
  - Due to increase in bioavailability of triptans
  - Small risk of serotonin syndrome in patients taking triptans concurrently with SSRIs, SNRIs, or St. John's wort
  - Theoretical risk of additive vasoconstriction and possible significant coronary vasoconstriction with combined use of triptans and ergot derivatives
  - Combination is generally contraindicated

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Best Pract J. 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Triptans - Precautions

- Limit use to ≤2 days/week
- Do not use within 24 hour of ergotamine derivatives, other triptans, or methysergide
- Screen for asymptomatic cardiac disease in patients at risk
  - Contraindicated in patients with risk of heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension
- Common adverse events:
  - Transient feelings of pain or tightness in the chest or throat
  - Tingling
  - Heat
  - Flushing
  - Heaviness or pressure
  - Drowsiness
  - Fatigue
  - Malaise

IM = intramuscular; IV = intravenous; SC = subcutaneous

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

Cardiovascular Safety of Triptans

- All triptans are associated with “triptan sensations”
  - Burning, tingling, or tightness in the face, neck, limbs, or chest[1]
- Patients may be alarmed by chest pain (3-5% of patients)[1,2]
  - Triptan dose may be lowered in sensitive patients[1]
- Serious cardiovascular events associated with triptans[1]
  - Patients with multiple cardiac risk factors may need cardiac evaluation before starting triptan therapy[1]

1. Best Pract J. 2014;62:28-36 http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf ; Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4:70-81; 2. Belvís R. *et al. Recent Pat CNS Drug Discov.* 2009;4:70-81.

Triptans and Serotonin Syndrome

- Potential risk with concurrent use of triptans and SSRIs
  - Interaction appears to be rare
- According to the American Headache Society, there is insufficient evidence to support limiting the use of triptans with SSRIs or SNRIs
- If used with SSRIs or SNRIs, monitor for symptoms of serotonin syndrome (weakness, hyperreflexia, poor coordination)
- Possible risk of serotonin syndrome if St. John's Wort and triptans are taken concurrently

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

1. *Best Pract J.* 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Withdrawing Triptans

- Triptan overuse → medication overuse headache, necessitating withdrawal
- Most strategies involve abrupt withdrawal of the triptan and the use of other medicines to manage symptoms
- Medications useful during withdrawal include naproxen, prednisone, metoclopramide or domperidone
- Prophylactic medicines for migraines may be required
- Headaches often improve within two months following withdrawal
  - Symptoms usually get worse before this improvement is seen
- Triptans may need to be reintroduced for acute migraine

Review patient after two to three weeks to ensure withdrawal has been achieved.

Neurology referral may be useful for patients unable to withdraw from medication.

Best Pract J. 2014;62:28-36. http://www.bpac.org.nz/BPJ/2014/July/docs/BPJ62-triptans.pdf

Pharmacokinetic Properties of Triptans

Triptan	Onset of Efficacy (min)	Time to Peak Levels (h)	Lipophilicity	Bioavailability (%)	Elimination $t_{1/2}$ (h)	Elimination Routes
Almotriptan	45-60	1.5-2.5	Unknown	80	3.5	Hepatic (active metabolite) Renal, MAO, CYP
Eletriptan	60	1.3.-2.8	High	50	4-5	Hepatic (active metabolite) CYP
Frovatriptan	Up to 4 hours	2-4	Low	24-30	26	Hepatic, CYP
Naratriptan	Up to 4 hours	2-3.5	High	63-73	5-6	Hepatic, renal, CYP
Rizatriptan	30	1	Moderate	45	2-2.5	Hepatic, MAO, renal
Sumatriptan	45-60	2-3	Low	14	2-2.5	Hepatic, MAO
Zolmitriptan	45-60	1-1.5	Moderate	40-48	2.5-3	Hepatic (active metabolite) MAO, CYP

Rizatriptan provides the fastest onset of efficacy

CYP = cytochrome hepatic system; MAO = monoamine oxidase A

Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4(1):70-81.

Efficacy Parameters of Oral Triptans

Triptan	Headache Response at 2 h (%)	Complete Relief of Pain at 2 h (%)	2 h Therapeutic Gain (%)	Recurrence Rate at 24 h (%)
Almotriptan 12.5 mg	57-65	20-25	26-32	18-27
Eletriptan 40 mg	65	29	22-41	19-23
Eletriptan 80 mg	65-80	37	30-53	21-33
Frovatriptan 2.5 mg	38-40	23-28	16-19	7-25
Naratriptan	45-52	21-27	21-22	17-28
Rizatriptan	70-77	40-44	27-40	28-47
Sumatriptan	50-61	30-32	29-36	29-34
Zolmitriptan 2.5 mg	64	33	34	13-39
Zolmitriptan 5 mg	65	38	37	24-32

Rizatriptan provides the best headache response and complete relief of pain at 2 h

Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4(1):70-81.

Selecting a Triptan – TRIPSTAR

Main Attribute	Definition	Lower Level Attributes
Efficacy	Extent to which an oral triptan can achieve and maintain pain-free status	Pain-free at 1 hour Pain-free at 2 hours Sustained pain-free*
Consistency of effect	Extent to which an oral triptan is efficacious in at least 2 of 3 migraine attacks	
Tolerability	Extent to which patients remain free of AEs	Freedom from CNS AEs† Freedom from CV AEs Freedom from other AEs

*Pain-free by 2 h post-dose, without recurrence of moderate or severe headache and without use of headache rescue medication 2-24 h post-dose

†asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, speech disorder, abnormal thinking, tremor, vertigo, other focal neurological symptom

AE = adverse event; CNS = central nervous system; CV = cardiovascular

Lipton RB *et al. Curr Med Res Opin.* 2005;21(3):413-24.

Selecting a Triptan – TRIPSTAR

- According to migraine sufferers and physicians:
  - Efficacy more important than tolerability or consistency
  - Freedom from CV events was most important tolerability attribute
- **Pain free at 1 hour** was the most important lower-level efficacy attribute for **migraineurs**
- **Sustained pain free** was the most important lower-level efficacy attribute for **physicians**
- Almotriptan, eletriptan, and rizatriptan were closest to hypothetical ideal triptan according to migraineurs, neurologists, and primary care providers

CV = cardiovascular

Lipton RB *et al. Curr Med Res Opin.* 2005;21(3):413-24.

Ergot Alkaloids as Acute Migraine Therapy

- First specific agents indicated for acute treatment of migraine
  - Use declined with introduction of triptans
- Ergotamine tartrate and dihydroergotamine mesylate are available as injectable and nasal spray formulations

- **Mechanism of action** includes multireceptor action at serotonergic subtypes 5-$HT_{1A,D,F,B}$ and 5-HTs
  - Leads to effects on neuropeptide release and neurogenically induced inflammation
  - Activity at alpha-adrenergic and dopaminergic systems may also contribute to action (but results in more side effects)

HT = hydroxytryptamine

Demaagd G. *P T.* 2008;33(7):404-16.

Ergot Alkaloids as Acute Migraine Therapy

- Inexpensive
- Long history of use for treatment of migraines

- Complex pharmacology
- Potential interactions with triptans, serotonergic drugs, inhibitors of CYP450 3A4
- Erratic pharmacokinetics
- Lack of evidence regarding effective doses
- Potent and sustained generalized vasoconstrictor effects
- High risk of overuse
- High risk of medication overuse headache

Demaagd G. *P T.* 2008;33(7):404-16; Goadsby PJ *et al. N Engl J Med.* 2002;346(4):257-70.

Possible Adverse Effects of Ergot Alkaloids

- Nausea and vomiting
- Muscle cramps
- Tingling in extremities
- Sense of difficulty swallowing
- Chest discomfort
- Nasal congestion
- Depression
- Fatigue
- Ergotism with prolonged use or overuse

Demaagd G. *P T.* 2008;33(7):404-16.

Ergot Alkaloids – Precautions

- Limit use to ≤2 days/week
- Do not use within 24 hours of other ergotamines or triptans
- Screen for asymptomatic cardiac disease in patients at risk
- **Do not combine with CYP 3A4 inhibitors** (*e.g.*, macrolide antibiotics and protease inhibitors
  - Potential risk for serious toxicity including vasospasm
- Fibrotic complications
  - Retroperitoneal and/or pleuropulmonary fibrosis
  - Fibrotic thickening of aortic, mitral, tricuspid and/or pulmonary valves

IM = intramuscular; IV = intravenous; SC = subcutaneous

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014; Paladin Labs Inc. Bellergal® Spacetabs product monograph. Revised February 13, 2014.

Ergot Alkaloids - Contraindications

- **Contraindicated** in patients with risk of heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension
- **Contraindicated** with concomitant ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole, or other vasoconstrictors

IM = intramuscular; IV = intravenous; SC = subcutaneous

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Pharmacologic Management of Migraine – Prophylaxis

Preventative Treatment: Mechanism-based Management of Migraine

Goals of Migraine Prophylaxis

- Reduce attack frequency
- Reduce attack severity
- Reduce attack duration
- Improve responsiveness to treatment of acute attacks
- Improve function
- Reduce disability

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Prophylactic Therapy in Migraine

- Must be individually tailored to each patient
- Consider:
  - Degree of disability
  - Demands
  - Expectations
  - Previous medication history
  - Migraine subtype
  - Comorbid disorders

There is no uniformly accepted criterion for the timing of preventative treatment

Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57.

EFNS Guidelines for Initiating Migraine Prophylaxis

Consider and discuss prophylactic therapy with patient when:

- Quality of life, business duties, or school attendance are severely impaired
- Patient experiences ≥2 attacks month
- Migraine attacks do not respond to acute drug treatment
- Frequent, very long, or uncomfortable auras occur

Migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by ≥50% within 3 months

EFNS = European Federation of Neurological Societies

Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

Principles of Migraine Prophylaxis

- Base choice of medication on
  - Diagnosis
  - Efficacy
  - Adverse event profile
  - Coexistent conditions
- Start low, go slow
  - Benefit develops slowly
- If first medication fails, choose one from a different class
- Monotherapy is preferred, but combination therapy is often necessary
- Communicate with the patient so he or she has realistic expectations for the treatment

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

Principles of Migraine Prophylaxis

- **Start low, go slow**
- Use an adequate trial period (unless there are AEs)
  - Medications may take 2 to 3 months to work
- Avoid interfering medications
  - Overuse of acute medications can hinder effectiveness
- Use of long-acting formulations may improve adherence
- Reevaluate therapy and consider tapering or discontinuing treatment after a period of stability
- Some preventative medications have teratogenic effects and their use should be avoided in women of childbearing age

AE = adverse event

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

Prophylactic Therapies in Migraine

- Major prophylactic anti-migraine drugs were not developed specifically for migraine
- Four major classes
  - Beta-blockers
  - Anti-convulsants
  - Serotonin receptor blockers
  - Calcium antagonists
- Others
  - Metabolic enhancers (*e.g.*, riboflavin, co-enzyme Q10)
  - Angiotensin converting enzyme inhibitors (*e.g.*, lisinopril)
  - Angiotensin converting enzyme receptor inhibitors (*e.g.*, candesartan)
  - Magnesium salts
  - Herbs (*e.g.*, petasites [butterbur], tanacetum parthenium [feverfew]

Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57.

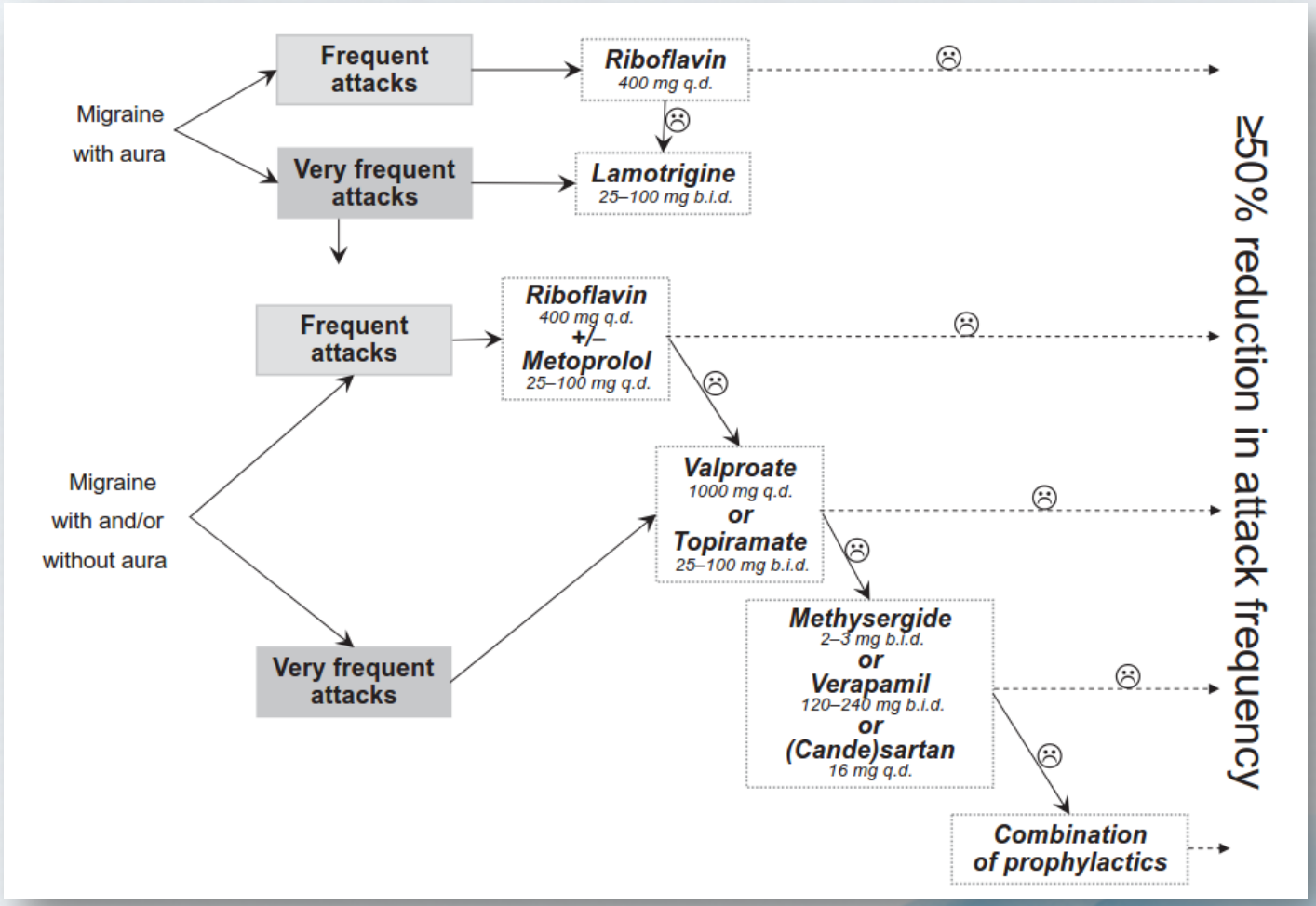
Prophylactic Drugs for Migraine

Drug(s)	Comments
Beta-blockers	• Most widely used drugs for migraine prophylaxis • 60 to 80% effective in decreasing migraine frequency by >50% • Similar efficacy to topiramate • Good tolerability • Excellent choice for patients with hypertension, CAD
Antidepressants	• TCAs most studied • Amitriptyline decreases number and intensity of migraines by 50 to 70%
Topiramate	• Rapid onset of action (within first month) • Shown to decrease mean monthly migraine periods • Good tolerability in most patients
Botox	• FDA approved therapy for migraine • Significantly reduces headache days/month vs. placebo • Few associated adverse events
Gabapentin	• $A_2\delta$ ligand with analgesic and anticonvulsant effects • Shown to significantly decrease 4-week migraine rate vs. placebo • No difference in adverse events vs. placebo

CAD = coronary artery disease; TCA = tricyclic antidepressant

Demaagd G. *P T.* 2008;33(7):480-7; Arulmozhi DK *et al. Vascul Pharmacol.* 2005;43(3):176-87; Silberstein SD. *Adv Stud Med.* 2005;5(6E):S666-S675; Garza I, Swanson JW. *Neuropsychiatr Dis Treat.* 2006;2(3): 281-91; Demaagd G. *P T.* 2008;33(7):480-7; Dodick DW *et al. Headache*. 2010 Jun;50(6):921-36; Allergan. BOTOX® (onabotulinumtoxinA) Prescribing Information, February 2014; Mathew NT *et al. Headache*. 2001 Feb;41(2):119-28.

Algorithm for "Stratified" and "Step-wise" Migraine Prophylaxis



Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57.

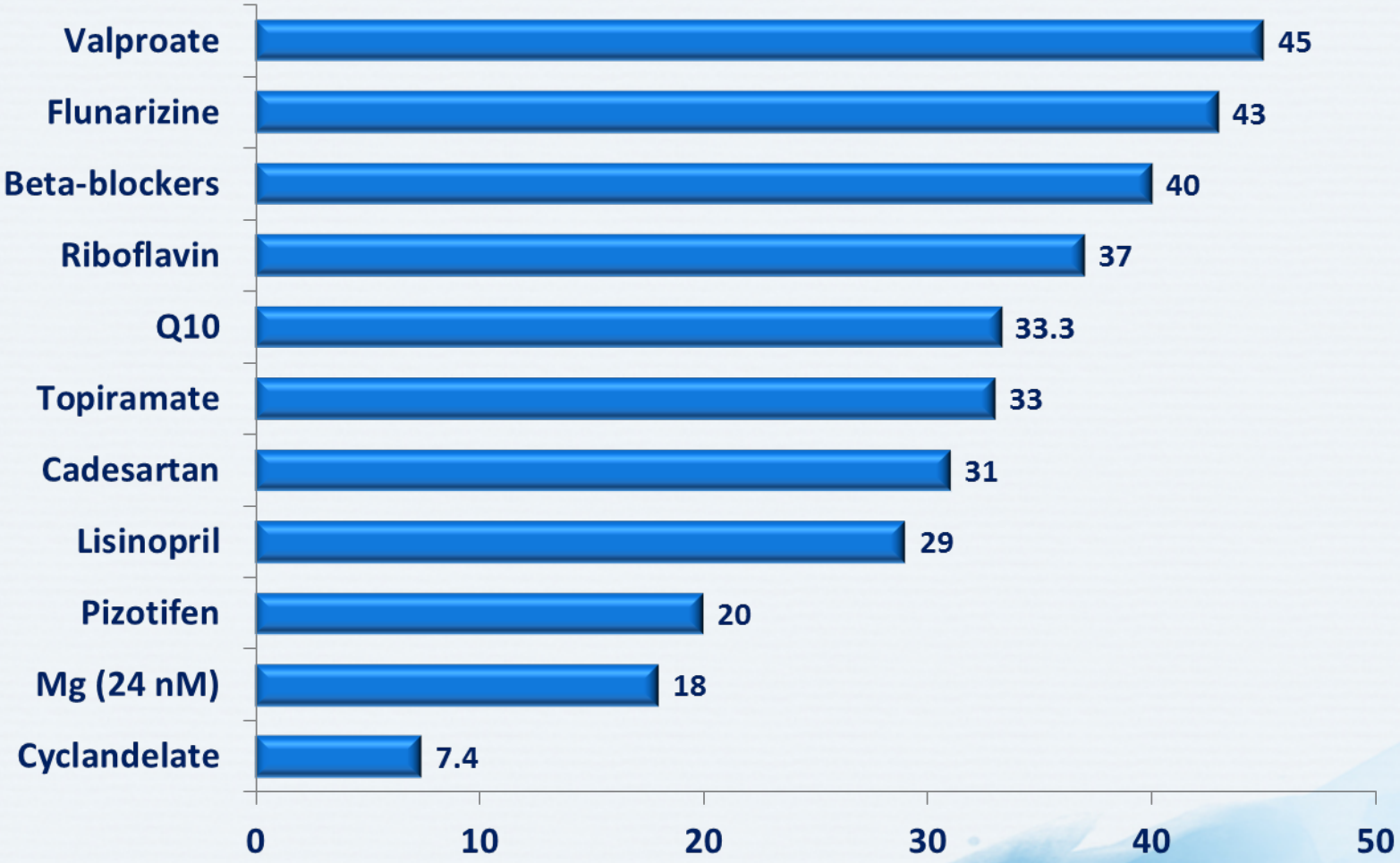
Prophylactic Pharmacotherapies for Migraine

Drug Class	Agent, Dose Range	Monitoring Parameter
Beta blockers	Propranolol (Inderal)* 40–240 mg/day in divided doses or LA q.d. Nadolol (Corgard) 20–120 mg q.d. or b.i.d. Timolol (Blocadren)* 20–60 mg q.d. or b.i.d. Atenolol (Tenormin) 25–100 mg q.d. Metoprolol (Toprol) 50–200 mg b.i.d.	Side effects • Heart rate • Blood pressure • Sexual dysfunction (males) Drug interactions Efficacy
Antidepressants	Tricyclic agents • Amitriptyline 10–150 mg h.s. • Nortriptyline (Pamelor) 10–150 mg h.s. • Doxepin (Sinequan) 10–200 mg h.s. • Desipramine (Norpramin) 25–150 mg h.s. MAOIs: Phenelzine (Nardil) 15–60 mg t.i.d. SSRIs: Fluoxetine (Prozac) 10–80 mg q.d.	Side effects • Anticholinergic • Cardiac status/predose ECG in some patients • Weight gain Drug interactions Efficacy
Anticonvulsants	Valproic acid (Depakene):* start 250 mg h.s. or b.i.d., titrate dose to 1,500 daily in divided doses Divalproex sodium 1,000 mg q.d. • Depakote valproate sodium • Depakene solution Topiramate (Topamax)* 100–400 mg b.i.d.–t.i.d. daily	Side effects • Sedation/fatigue • Liver enzymes • Complete blood count Drug interactions Efficacy Cognitive effects
Calcium-channel blockers	Verapamil (Calan) 240–360 mg daily in divided doses	Side effects • Heart rate • Blood pressure • Sexual dysfunction (males) Drug interactions Efficacy
NSAIDs	Naproxen sodium (Naprosyn) 550–1,100 mg daily in divided doses Ketoprofen 150 mg daily in divided doses	Side effects • Renal function • Signs and symptoms of bleeding

*These agents are FDA-approved for migraine prophylaxis.
b.i.d. = twice daily; ECG = electrocardiogram; ER = extended-release; h.s. = at bedtime; LA = long-acting; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; q.d. = once daily; t.i.d. = three times daily.

Demaagd G. *P T.* 2008;33(7):480-7

Therapeutic Gain in Migraine Preventative Treatment*



*% of "responders", with a reduction of minimum 50% of attacks

Fumal A, Schoenen J. *Neuropsychiatr Dis Treat.* 2008;4(6):1043-57.

Beta-blockers in Migraine Prophylaxis

- Most widely used class of drugs in migraine prophylaxis
  - Considered drug of choice for migraine prevention
  - 60 to 80% effective in producing a >50% reduction in attack frequency
  - Comparison trials with β-blockers and other preventative therapies, including topiramate, have reported similar efficacy, sometimes with better tolerability

Demaagd G. *P T.* 2008;33(7):480-7; Arulmozhi DK *et al. Vascul Pharmacol.* 2005;43(3):176-87.

Beta-blockers in Migraine Prophylaxis

- **Mechanism of action** is uncertain
  - May be due to inhibition of β1-mediated mechanisms
    - Inhibition of norepinephrine release by blocking prejunctional β receptors
  - Delays tyrosine hydroxylase activity in superior cervical ganglia
- Action is probably central and could be mediated by:
  - Inhibiting central β receptors interfering with vigilance-enhancing adrenergic pathway
  - Interaction with serotonin receptors
  - Cross modulation of serotonin system

Demaagd G. *P T.* 2008;33(7):480-7; Arulmozhi DK *et al. Vascul Pharmacol.* 2005;43(3):176-87.

Beta-blockers in Migraine Prophylaxis

Usually well tolerated

- Side effects include
  - Sedation
  - Dizziness
  - Vivid dreams
  - Depression
  - Fatigue
  - Orthostatic hypotension
  - Impotence

Absolute contraindications

- Asthma
- Heart block
- Severe peripheral vascular disease
- Raynaud's phenomenon

Drug interactions

- Other cardiovascular drugs that influence heart rate or blood pressure
- Propanolol inhibits triptan metabolism, increasing the risk of side effects

β-blockers are an excellent choice for patients with comorbidities, including hypertension and coronary artery disease

Demaagd G. *P T.* 2008;33(7):480-7; Arulmozhi DK *et al. Vascul Pharmacol.* 2005;43(3):176-87.

TCAs as Migraine Prophylaxis

- The most studied of the antidepressants for migraine prevention
- Amitriptyline may reduce number and intensity of attacks by 50 to 70% at daily doses of 10 to 100 mg
- Amitriptyline has shown similar efficacy to propranolol
- Proposed **mechanism of action**
  - Thought to involve inhibition of central cortical depression and sympathetic activity associated with migraine pathophysiology

TCAs are a first-line option for in patients without contraindications
May be excellent for patients who also suffer from depression, anxiety, or insomnia

TCA = tricyclic antidepressant

Demaagd G. *P T.* 2008;33(7):480-7.

Safety of TCAs in Migraine Prophylaxis

Possible adverse events

- Dry mouth
- Constipation
- Urinary retention
- Weight gain
- Central effects (sedation, weakness, fatigue, tremor)

Potential serious adverse events

- Cardiac events (*e.g.*, sinus tachycardia, corrected QT (QTc) prolongation)
- Blood pressure fluctuations

Drug interactions

- Other central-acting agents
- Cholinergic drugs
- Serotonergic agents

CONTRAINDICATIONS: angle-closure glaucoma, urinary retention, orthostatic hypotension

TCA = tricyclic antidepressant

Demaagd G. *P T.* 2008;33(7):480-7.

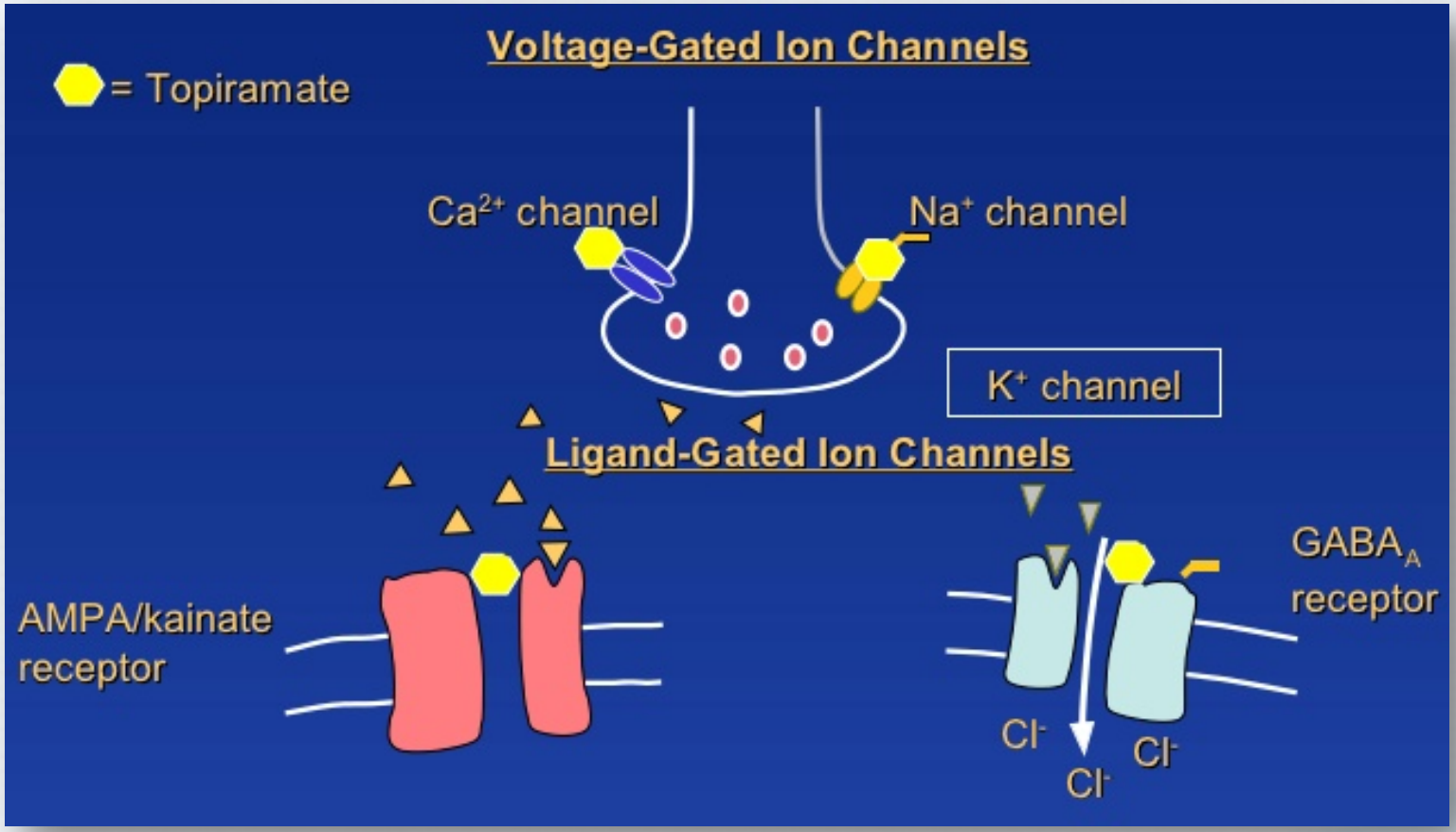
Topiramate as Migraine Prophylaxis

- Anti-epileptic drug: sulfamate-substituted D-fructose
  - Readily enters CNS
- Rapid onset of action – within first month of treatment
- Reduces mean monthly migraine periods (100 or 200 mg/day)
  - Some patients may require 600 or 800 mg/day
  - Titrate up slowly
  - If adverse events become intolerable, titrate more slowly or reduce dose

CNS = central nervous system

Silberstein SD. *Adv Stud Med.* 2005;5(6E):S666-S675; Garza I, Swanson JW. *Neuropsychiatr Dis Treat.* 2006;2(3): 281-91; Demaagd G. *P T.* 2008;33(7):480-7.

Topiramate Mechanism of Action



Shank RP *et al. Epilepsia*. 2000;41 Suppl 1:S3-9.

Safety of Topiramate in Migraine Prophylaxis

Good tolerability in most patients

Possible **adverse events**

- Kidney stones
- Myopia with angle-closure glaucoma
- Sedation
- Cognitive changes
- Weight loss
- Nausea
- Taste perversion
- Loss of appetite
- Paresthesias
- Fatigue
- Diarrhea

Drug interactions

- Other central-acting drugs
- Antidepressants
- Oral contraceptives

- **Patients taking topiramate must be monitored regularly**
- **Patients taking topiramate should be advised of its potential for visual and cognitive changes and their need to ensure adequate hydration**

Silberstein SD. *Adv Stud Med.* 2005;5(6E):S666-S675; Garza I, Swanson JW. *Neuropsychiatr Dis Treat.* 2006;2(3): 281-91; Demaagd G. *P T.* 2008;33(7):480-7.

Sodium Divalproate as Migraine Prophylaxis

- Anticonvulsant
- First-line agent in migraine prevention
- Initial dose is usually 250 mg daily, titrated to 1500 mg
  - Dose escalation is usually not helpful
- Special indications:
  - Prolonged or atypical migraine aura
  - Tension-type headache
  - Concurrent epilepsy, mania, trigeminal neuralgia, cluster headache

Generally well tolerated as monotherapy or in polytherapy for migraine and cluster headaches

Parsekyan D. *West J Med.* 2000;173:341-5; Gallagher RM, Mueller LL, Freitag FG. *J Am Osteopath Assoc.* 2002;102:92-4.

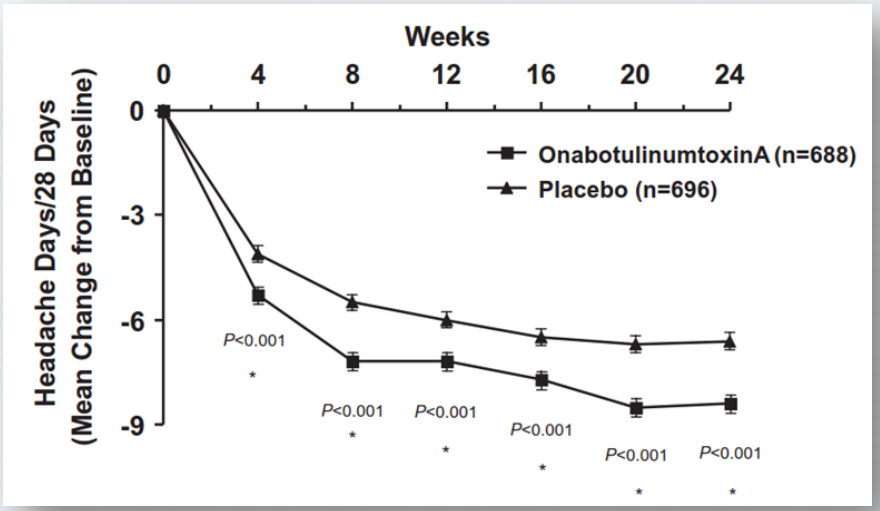
Sodium Divalproate as Migraine Prophylaxis – Precautions

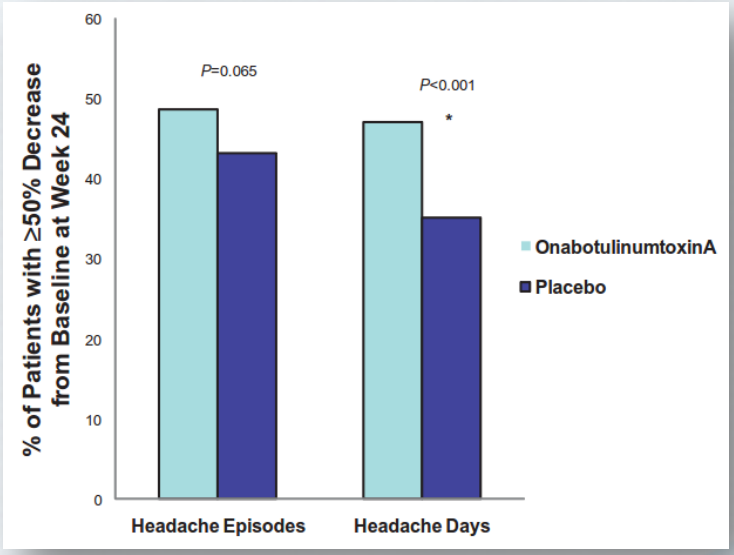
Side Effects	Precautions
• Nausea • Vomiting • Tremor • Weight gain • Hair loss • Drowsiness • Ataxia • Hepatotoxicity	• Liver disease • Thrombocytopenia • Pregnancy • Young children (high risk of hepatotoxicity)

Parsekyan D. *West J Med.* 2000;173:341-5.

OnabotulinumtoxinA as Migraine Prophylaxis

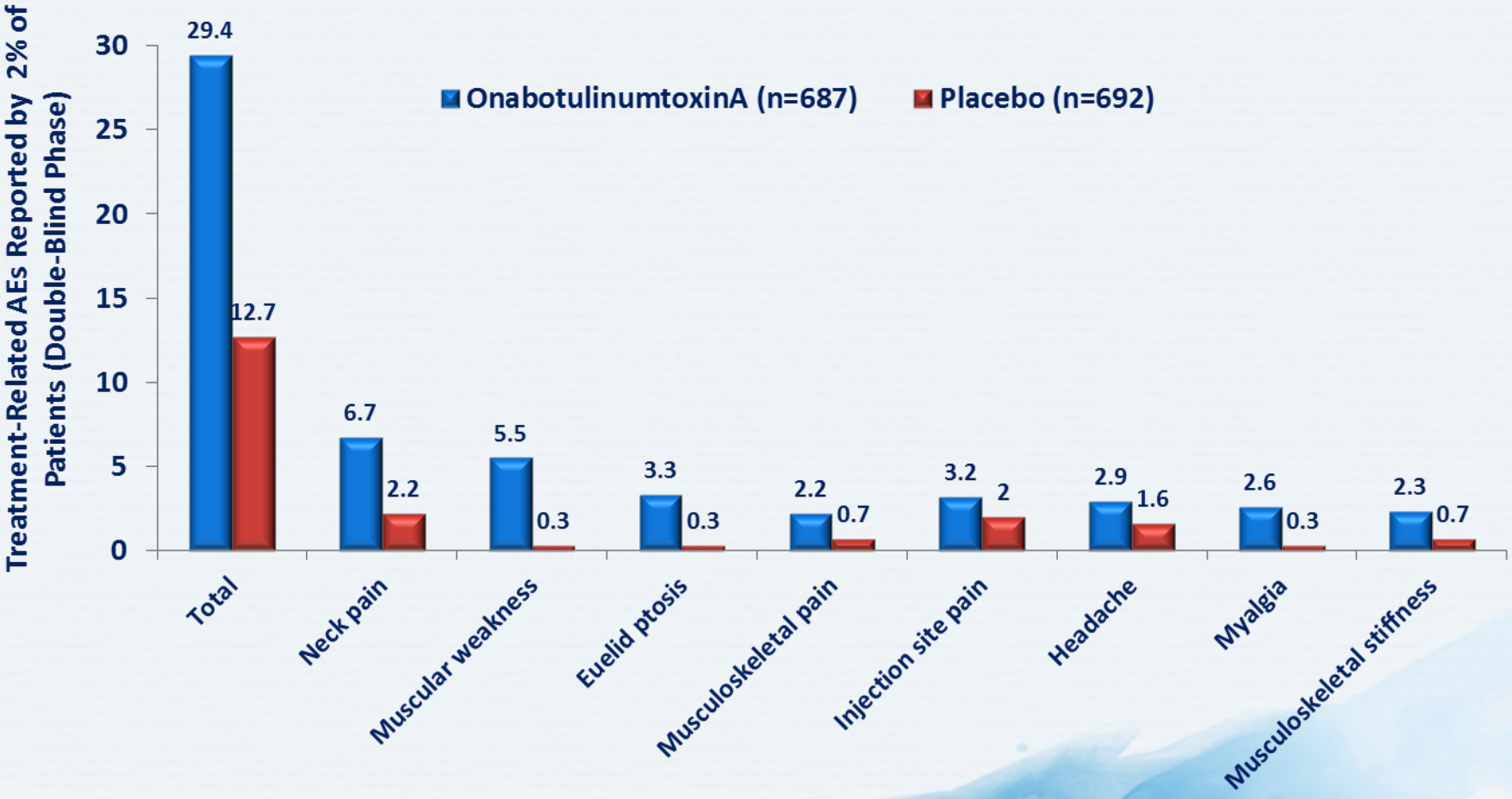
FDA-approved preventative migraine treatment





Dodick DW *et al. Headache*. 2010 Jun;50(6):921-36; Allergan. BOTOX® (onabotulinumtoxinA) Prescribing Information, February 2014.

OnabotulinumtoxinA as Migraine Prophylaxis



AE = adverse event

Dodick DW *et al. Headache*. 2010 Jun;50(6):921-36.

MOA of OnabotulinumtoxinA in Migraine Prophylaxis

- Precise MOA has not been fully determined
- Blocks release of neurotransmitters associated with pain
  - May inhibit peripheral signals to central nervous system
    - →Indirect inhibition of central sensitization
- Persons with higher frequency of migraines are more susceptible to adverse consequences of central sensitization
  - Treatments that block central sensitization may help

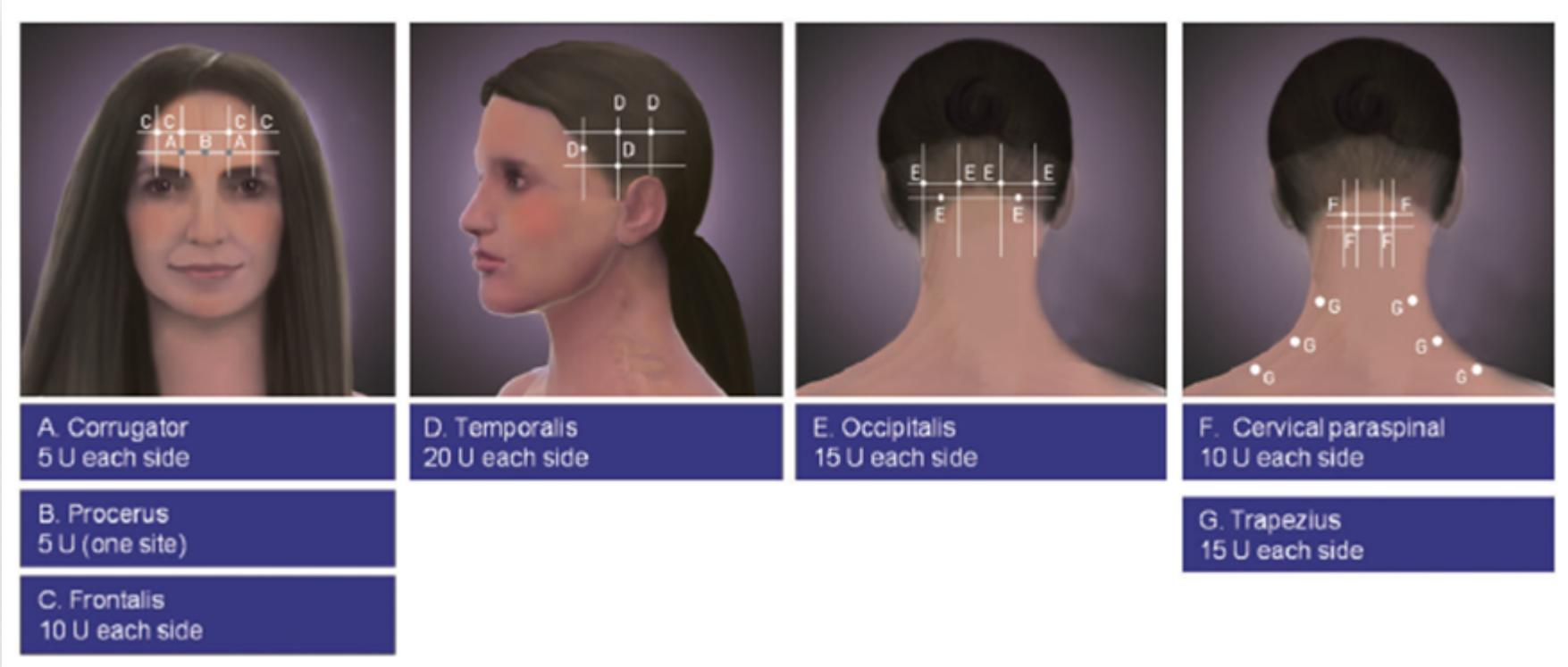
*For example, substance P, calcitonin gene-related peptide (CGRP), glutamate
MOA = mechanism of action
Dodick DW *et al. Headache*. 2010 Jun;50(6):921-36.

When Can We Use OnabotulinumtoxinA (Botox®) Prophylaxis in Chronic Migraine?

- Headache days of ≥15 days/month for the last 3 months
- ≥8 episodes of migraine/month (within 15 days of headache/month)
- In chronic migraine patients without medication overuse headache

Acta Neurol Scand. 2014 Jan;129(1):61-70. doi: 10.1111/ane.12171. Epub 2013 Sep 20.
OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program.
Aurora SK1, Dodick DW, Diener HC, DeGryse RE, Turkel CC, Lipton RB, Silberstein SD.

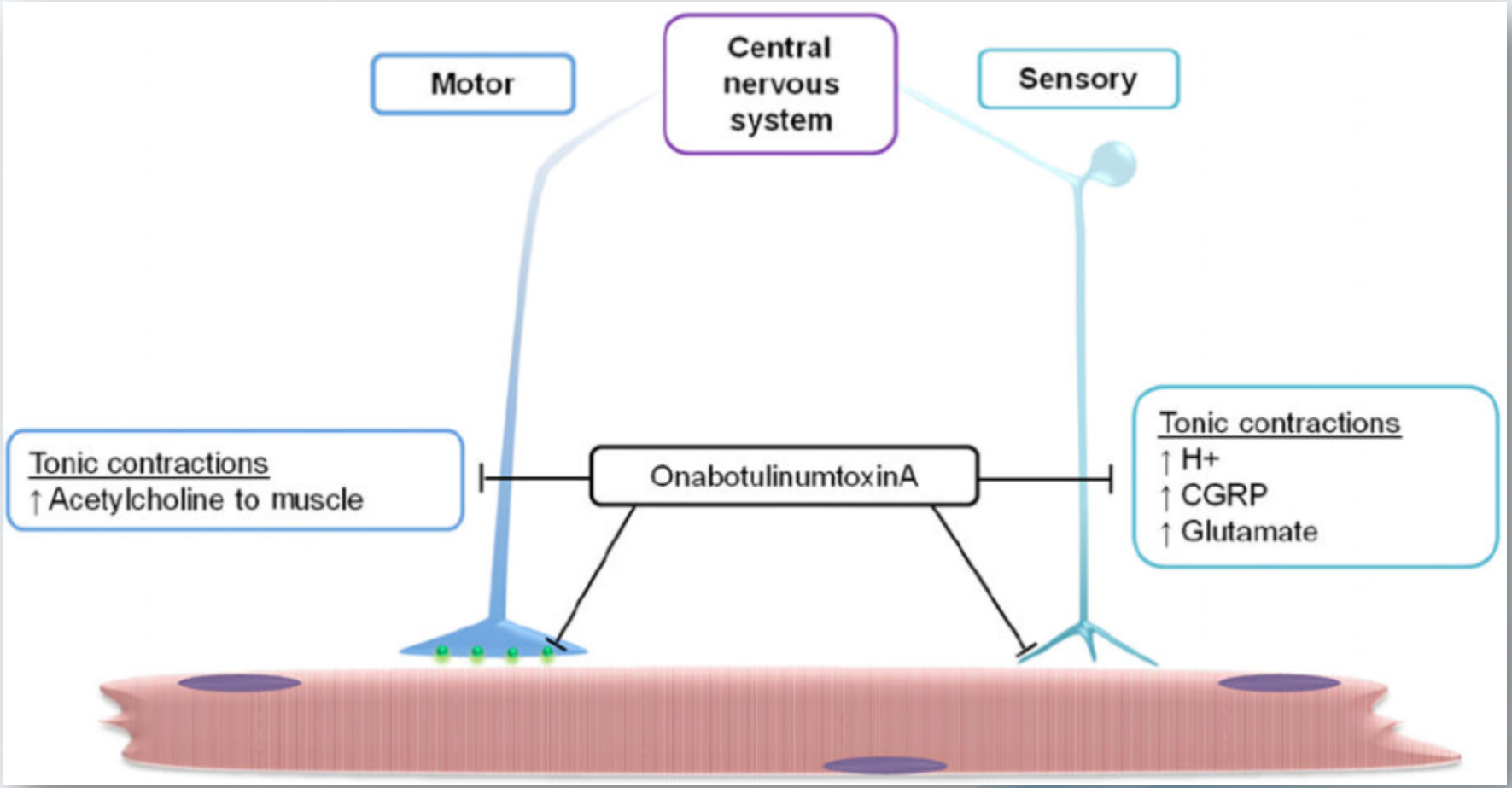
OnabotulinumtoxinA (Botox®) Injections*



*Every 12 weeks, 155-190 units

Blumenfeld A *et al. Headache*. 2010;50:1406-18.

Mechanism of OnabotulinumtoxinA in Chronic Migraine



Durham PL, Cady R. *Headache*. 2011;51:1573-7.

SNRIs as Migraine Prophylaxis

- SSRIs and SNRIs are no better than placebo for reducing the number of migraine attacks
- No differences in minor side effects between SSRIs or SNRIs vs. placebo
- SSRIs and SNRIs offer no advantages when compared to other active treatments, specifically the amitriptyline
- Fewer minor side effects with SSRIs or SNRIs than with amitriptyline but side effects do not influence discontinuation of any of these drugs
- No studies exist comparing SSRIs or SNRIs with pharmacological treatments other than antidepressants

Banzi R *et al.Cochrane Database Syst Rev.* 2015 Apr 1;4:CD002919. [Epub ahead of print]

Calcium Channel Blockers as Migraine Prophylaxis

- Effective second-line agents
- Usually slower in onset than β-blockers
- Initial increase in headache frequency may occur on starting therapy

Viable alternative in patients who cannot tolerate β-blockers

Parsekyan D. *West J Med.* 2000;173:341-5; Gallagher RM, Mueller LL, Freitag FG. *J Am Osteopath Assoc.* 2002;102:92-4.

Calcium Channel Blockers as Migraine Prophylaxis – Precautions

Side Effects	Precautions
• Constipation • Dizziness • Hypotension • Peripheral edema • Weight gain	• Ventricular dysfunction • Heart block • Hypotension • Bradycardia • Sick sinus syndrome • Pregnancy

Parsekyan D. *West J Med.* 2000;173:341-5.

Angiotensin-II Receptor Blockers (ARBs) in Migraine Prophylaxis

- Target = renin angiotensin system (RAS)
- RAS has neurophysiological, chemical, and immunological effects relevant to migraine pathophysiology
- Candesartan (vs. placebo) reduced:
  - Mean number of days with headache
  - Days and hours with headache or migraine
  - Headache severity
  - Level of disability
  - Days of sick leave
- Generally well tolerated, no significant drug-drug interactions

ARBs may be useful in patients with frequent headaches who do not respond to conventional prophylactic agents

Tronvik E et al. JAMA. 2003;289:65-9; Gaur AR et al. Int J Res Dev Pharmacy Life Sci. 2013;5:553-8; Barreras A, Gurk-Turner C. *Proc (Bayl Univ Med Cent).* 2003;161:123-6.

Gabapentin as Migraine Prophylaxis

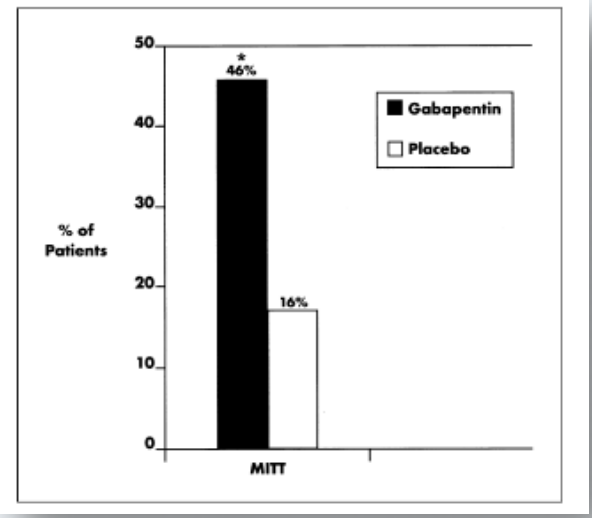
- $\alpha_2\delta$ ligand with anti-nociceptive and anticonvulsant effects
  - Has been used in treatment of neuropathic pain conditions
  - Dosage: 900 mg to 2400 mg three times daily (maximum daily = 3600 mg)
- Mechanism of action is not fully understood
  - Interacts with $\alpha_2\delta$ subunit of Ca^{2+}channels
  - Increases concentration and probably the rate of synthesis of γ-aminobutyric acid (GABA) in the brain
  - Analgesic effect may be due to its ability to bind to gabapentin-binding protein in the outer layers of cerebral cortex to inhibit monoamine neurotransmitter release
  - May operate at spinal cord level by altering N-methyl-D-aspartate responses

Mathew NT *et al. Headache*. 2001 Feb;41(2):119-28; Silberstein SD. *Adv Stud Med.* 2005;5(6E):S666-S675.

Gabapentin as Migraine Prophylaxis

Double-blind, placebo-controlled 12-week study of patients with migraine

- After 12 weeks, median 4-week migraine rate was 2.7 for the gabapentin-treated patients (2400 mg/day) and 3.5 for placebo-treated patients (P=0.006), vs. 4.2 and 4.1, respectively, during baseline period



Patients demonstrating ≥50% reduction in 4-week migraine rate (P=0.008)

- Significant reduction in 4-week headache rate with gabapentin (P=0.013).
- Most frequent **adverse events** for both groups: asthenia, dizziness, somnolence, and infection

Mathew NT *et al. Headache*. 2001 Feb;41(2):119-28; Silberstein SD. *Adv Stud Med.* 2005;5(6E):S666-S675.

Procedural Therapies for Migraine

Peripheral Nerve Blocks for Migraine

- Injections of local anesthetic agents to peripheral trigeminal and cervical nerve branches may provide prompt and definitive relief of acute head pain for days, weeks, or months
- Safe, well tolerated, no significant drug interactions, and few contraindications
- Typically provide relief that far outlasts their anesthetic effect
  - May be due to effects on central pain modulation
    - Associated symptoms (*e.g.*, photophobia, cutaneous allodynia) may be reduced
- A single greater occipital nerve injection is extremely effective in aborting an attack period in cluster headache

Robbins MS, Blumenfeld A. Peripheral nerve blocks for headaches. Available at: http://www.americanheadachesociety.org/assets/1/7/Andrew_Blumenfeld_and_Matthew_Robbins_-_Peripheral_Nerve_Blocks.pdf. Accessed March 18, 2015.

Potential Indications for Peripheral Nerve Blocks in the Treatment of Headache Disorders

Headache Disorder	Nerve(s) Blocked	Evidence
Primary headache disorders		
Migraine	GON, STN, SON	Retrospective[23-25] Prospective, noncontrolled[12,26]
Cluster headache	GON	Case series[4,13] Open label[14] Retrospective[15] Double blind, placebo controlled[7,8]
Chronic daily headache	GON	Case series[4] Open label[27] Prospective, noncontrolled[28] Prospective, randomized controlled[20]
Hemicrania continua	GON, SON	Case series[4,18]
New daily persistent headache	GON	Case series[4,29]
Secondary headache disorders		
Cervicogenic headache	GON, LON, SON	Case series[30,31] Retrospective[25] Prospective, noncontrolled[32] Prospective, comparative[33] Double blind, placebo controlled[34]
Post-traumatic headache	GON	Retrospective[35]
Post-dural puncture headache	GON, LON	Prospective, comparative[36]
Cranial neuralgias		
Supraorbital neuralgia	SON	Case series[37-39]
Auriculotemporal neuralgia	ATN	Case series[40]

ATN = auriculotemporal nerve; GON = greater occipital nerve; LON = lesser occipital nerve; SON = supraorbital nerve; STN = supratrochlear.nerve.

Blumenfeld A *et al*. *Headache*. 2013;53:437-46.

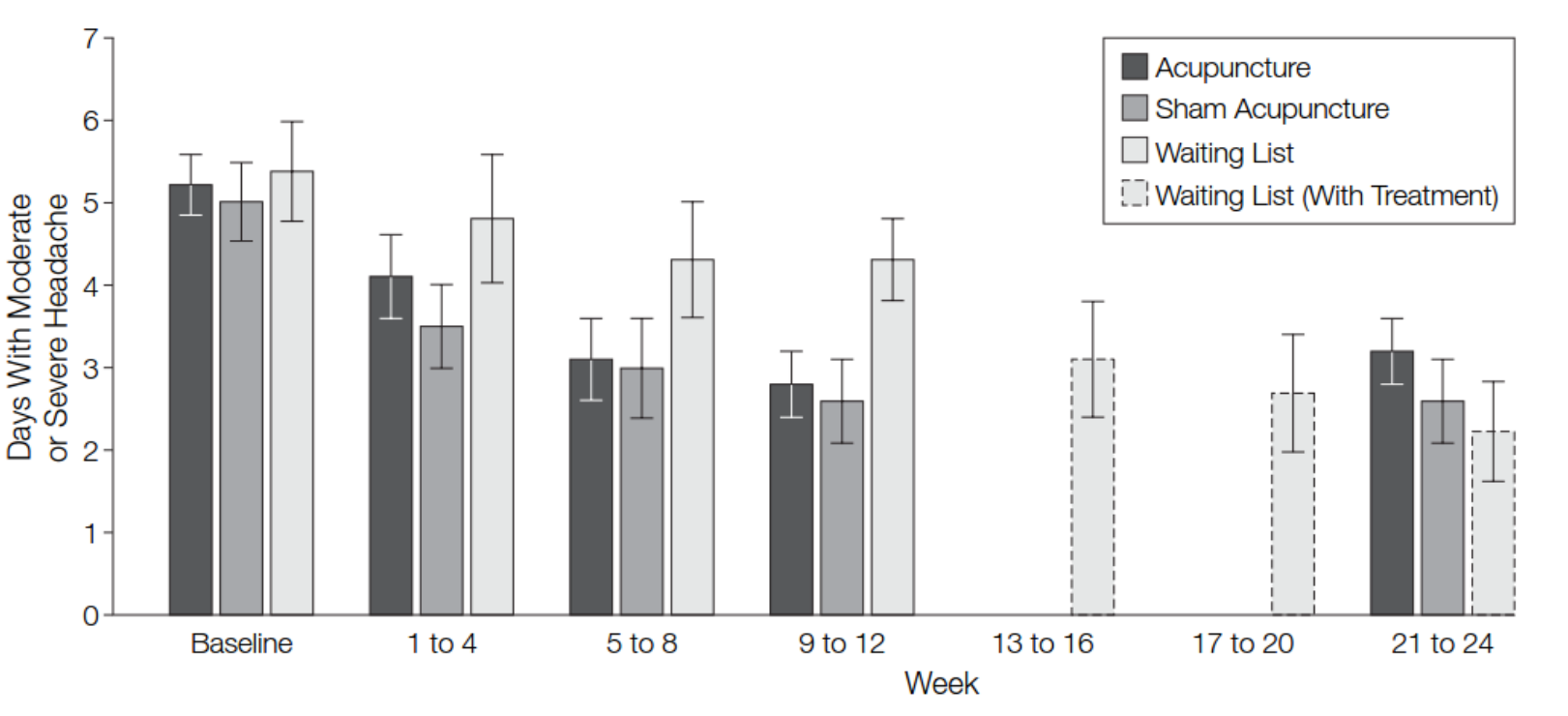
Potential Precautions and Contraindications for Peripheral Nerve Blocks in the Treatment of Headache Disorders

Patient Population	Concern	Action
Local anesthesia allergy	Allergic reaction, including anaphylaxis	PNB with local anesthetic contraindicated Use corticosteroids only[19]
Elderly	Hypotension Hypertension	Reduce concentration of anesthetic (avoid lidocaine 5%)[41] Limit number of nerves to be blocked in a single session Restrict PNB to unilateral GON injection if possible
Pregnancy	Teratogenicity	Use lidocaine (FDA Category B) over bupivacaine (FDA Category C) Avoid betamethasone and dexamethasone (accelerate fetal lung development) Caution is warranted in the use of any corticosteroids in the pregnant population
Prior vasovagal attacks Prior syncopal attacks	Vasovagal reaction Presyncope or syncope	Perform PNB in supine position, where feasible Use bupivacaine instead of lidocaine Reduce concentration of anesthetic agent Allow for extra time in the supine position after the procedure as a precaution
Open skull defect Craniotomy	Intracranial diffusion of anesthetic agent	PNB contraindicated[42,43]
Anticoagulation therapy Antiplatelet therapy	Hematoma	Extra attention to palpate for (and avoid) neighboring arteries (occipital, temporal) Compress at each PNB site for 5-10 minutes
Cosmetic concerns	Alopecia Cutaneous atrophy	Avoid corticosteroids If methylprednisolone must be used, dose <80 mg in GON region[10]

FDA = Food and Drug Administration; GON = greater occipital nerve; PNB = peripheral nerve block.

Blumenfeld A *et al*. *Headache*. 2013;53:437-46.

Acupuncture for Migraine Prophylaxis

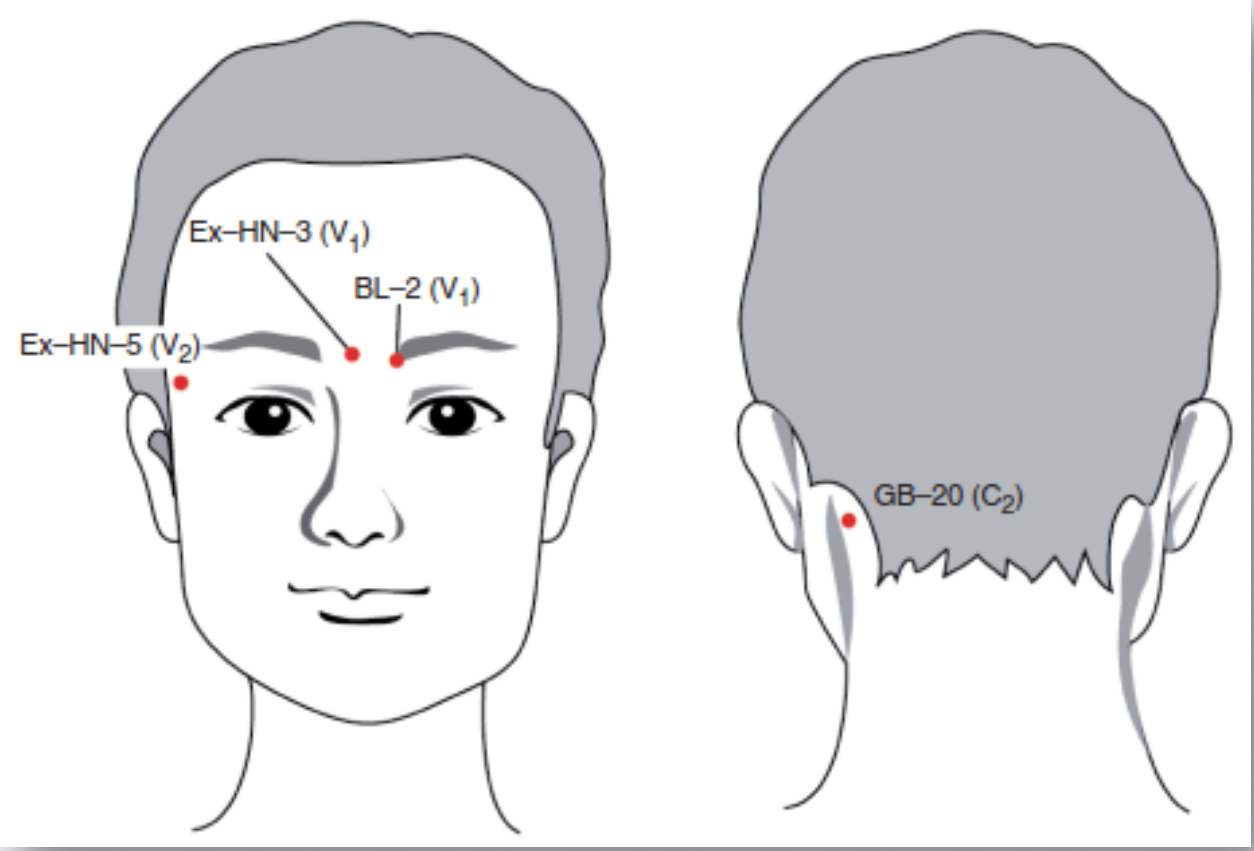


Acupuncture was no more effective than sham acupuncture in reducing migraines, although both interventions were more effective than a waiting list control

Error bars indicate 95% confidence interval

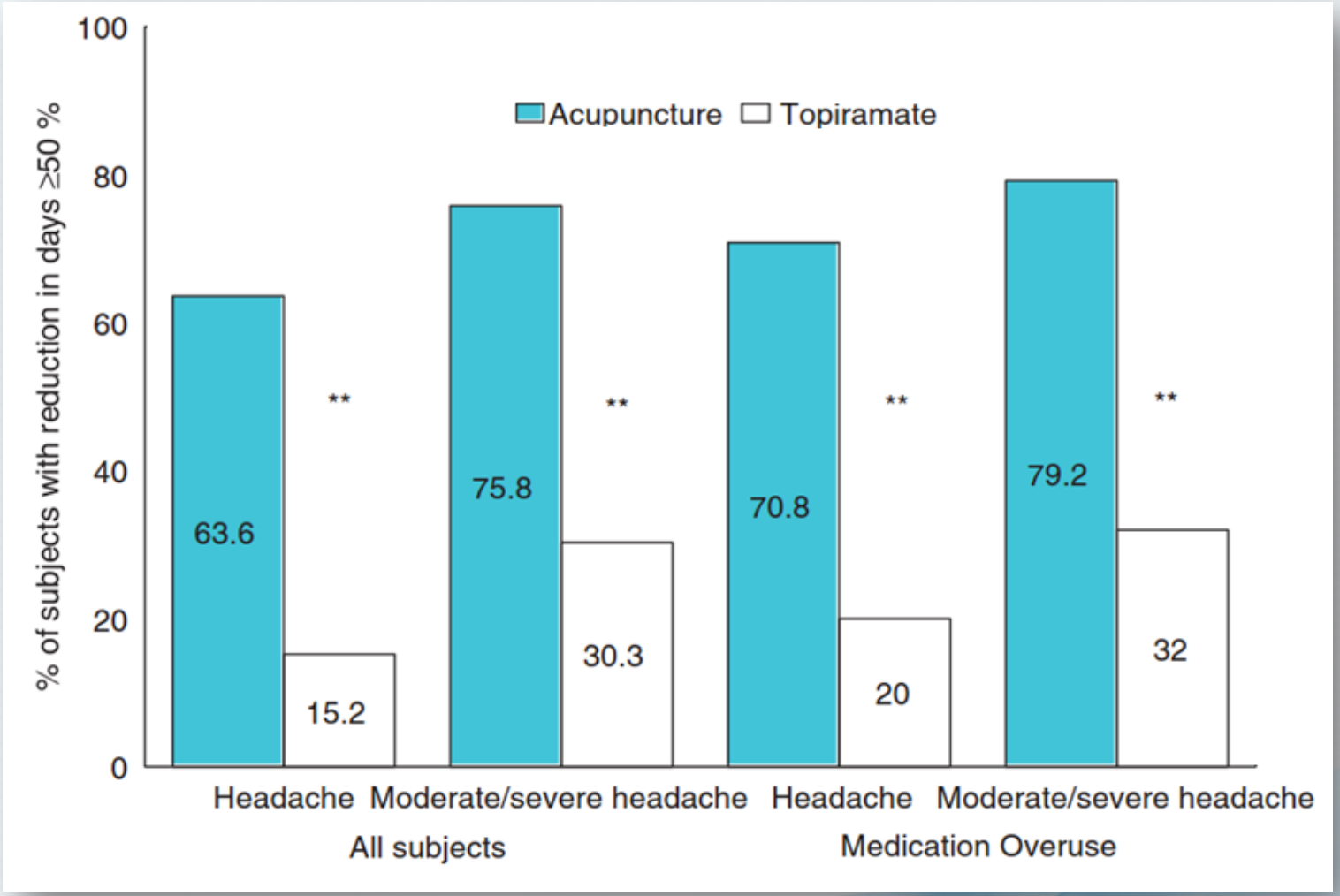
Linde K *et al. JAMA*. 2005;293(17):2118-25.

Acupuncture vs. Topiramate for Migraine Prophylaxis



Location of the acupoints used (all bilateral except Ex-HN-3, which is located at the head midline) and their relation to the dermatomes.
Dermatomes: V1 = ophthalmic branch of the trigeminal nerve; V2 = maxillary branch of the trigeminal nerve; C2 = dermatome of the second cervical nerve
Yang CP *et al. Cephalalgia.* 2011;31(15):1510-21.

Acupuncture vs. Topiramate for Migraine Prophylaxis



**P<0.01

Yang CP *et al. Cephalalgia.* 2011;31(15):1510-21.

When to Refer to a Specialist

- Doubt over diagnosis of migraine
- A rare form of migraine is suspected
- Diagnosis of cluster headache
- Other headaches besides migraine complicate the diagnosis
- Persistent management failure
- Migraines are getting worse or more frequent
- Suspicion of serious secondary headache or cases where investigation may be necessary to rule out serious pathology
- Comorbid disorders requiring specialist management
- Presence of risk factors for coronary heart disease may warrant referral to a cardiologist prior to initiating triptan therapy

The Migraine Trust. Migraine clinics. Available at: http://www.migrainetrust.org/factsheet-migraine-clinics-10783. Accessed March 18, 2015; Steiner TJ *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

Future Treatment Options for Migraine

Guidelines for the Pharmacological Management of Migraine

- **American Academy of Neurology/American Headache Society**
- **Canadian Headache Society**
- **Latin American Consensus**
- **EFNS**

AAN/AHS Guidelines for Episodic Migraine Prevention in Adults

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs	Antidepressants/ SSRI/SSNRI/TCA	ACE inhibitors	Carbonic anhydrase inhibitor	Established as not effective
Divalproex sodium	Amitriptyline	Lisinopril	Acetazolamide	Antiepileptic drugs
Sodium valproate	Venlafaxine	Angiotensin receptor blockers	Antithrombotics	Lamotrigine
Topiramate	β-Blockers	Candesartan	Acenocoumarol	Probably not effective
β-Blockers	Atenolol[a]	α-Agonists	Coumadin	Clomipramine[a]
Metoprolol	Nadolol[a]	Clonidine[a]	Picotamide	Possibly not effective
Propranolol	Triptans (MRM[b])	Guanfacine[a]	Antidepressants SSRI/SSNRI	Acebutolol[a]
Timolol[a]	Naratriptan[b]	Antiepileptic drugs	Fluvoxamine[a]	Clonazepam[a]
Triptans (MRM[b])	Zolmitriptan[b]	Carbamazepine[a]	Fluoxetine	Nabumetone[a]
Frovatriptan[b]		β-Blockers	Antiepileptic drugs	Oxcarbazepine
		Nebivolol	Gabapentin	Telmisartan
		Pindolol[a]	TCAs	
		Antihistamines	Protriptyline[a]	
		Cyproheptadine	β-Blockers	
			Bisoprolol[a]	
			Ca++ blockers	
			Nicardipine[a]	
			Nifedipine[a]	
			Nimodipine	
			Verapamil	
			Direct vascular smooth muscle relaxants	
			Cyclandelate	

AAN = American Academy of Neurology; ACE = angiotensin-converting-enzyme; AHS = American Headache Society; MRM = menstrually-related migraine; SSNRI = selective serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

[a]Classification based on original guideline and new evidence not found for this report

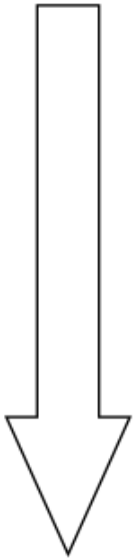
[b]For short-term prophylaxis of menstrually-related migraine

Silberstein SD *et al. Neurology.* 2012;78(17):1337-45.

CHS Guidelines for Acute Migraine Therapy

Acute Migraine Treatment Strategies and Medication Summary: General

Increasing migraine severity - Refractoriness to therapy



Clinical Phenotype	Strategy	Medications
Mild – moderate attack strategies	1.a Acetaminophen	Acetaminophen ± metoclopramide
	1.b NSAID	Ibuprofen, diclofenac potassium, naproxen sodium, ASA, all ± metoclopramide
Moderate – severe attack /NSAID failure strategies	2.a NSAID with triptan rescue	NSAID ± metoclopramide + a triptan later for rescue if necessary
	2.b Triptan	Triptan ± metoclopramide Sumatriptan (SC injection, nasal, oral) Zolmitriptan (nasal, oral, wafer) Rizatriptan (oral, wafer) Naratriptan (oral) Eletriptan (oral) Almotriptan (oral) Frovatriptan (oral)
Refractory migraine strategies	3.a Triptan – NSAID combination	Triptan + NSAID taken simultaneously ± metoclopramide
	3.b Triptan – NSAID combination with rescue	Triptan + NSAID taken simultaneously ± metoclopramide + one or more for rescue later (as necessary) of: Ketorolac IM Indomethacin (oral or rectal) Prochlorperazine (oral or rectal) Chlorpromazine (oral) Dexamethasone or prednisone Opioid combination analgesic
	3.c Dihydroergotamine	Dihydroergotamine (nasal or SC or IM self-injection) ± metoclopramide

CHS = Canadian Headache Society

Worthington I *et al. Can J Neurol Sci.* 2013;40(5 Suppl 3):S33-S62.

CHS Guidelines for Migraine Prophylaxis

Prophylactic Drug Treatment Strategies Based on Clinical Setting

1. First time strategies: (for the patient who has not had prophylaxis before)
   a. Beta-blocker strategy: propranolol, nadolol, metoprolol
   b. Tricyclic strategy: amitriptyline (nortriptyline)
2. Low side effect strategies:
   a. Drug: candesartan, lisinopril
   b. Herbal / vitamin / mineral: Magnesium citrate, riboflavin, butterbur, Coenzyme Q10
3. Increased body mass index strategy: topiramate
4. Hypertension strategy: propranolol, nadolol, metoprolol, candesartan, lisinopril
5. Depression / anxiety strategy: amitriptyline, venlafaxine, (nortriptyline) (dual therapy)
6. Additional monotherapy drug strategies: topiramate, divalproex, gabapentin, pizotifen, flunarizine, verapamil
7. Refractory patient strategy: concomitant use of two drugs
8. Migraine during pregnancy strategy: drug avoidance if possible. When necessary, magnesium, propranolol, metoprolol, amitriptyline and (nortriptyline) are considered relatively safe options (See section 3)
9. Migraine during lactation strategy: drug avoidance if possible. When necessary, magnesium, propranolol, nadolol, metoprolol, amitriptyline, (nortriptyline) and valproate** are considered compatible with breast feeding (See section 3).

*Drugs in brackets have insufficient evidence from randomized trial to routinely recommend their use. **Valproate is teratogenic, and should be avoided in women at risk for pregnancy.

CHS = Canadian Headache Society

Worthington I *et al. Can J Neurol Sci.* 2013;40(5 Suppl 3):S33-S62.

CHS Guidelines for Migraine Prophylaxis (1)

Recommended Dosages of Pharmacological Agents for Migraine Prophylaxis

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Antiepileptics:					
Divalproex sodium (also valproic acid or sodium valproate)	250 mg/d for 1 week, then 250 mg BID for 1 week, then 250 mg in am & 500 mg at bedtime; ↑ weekly by 250 mg, if needed	750-1500 mg/d (divided BID)	Liver disease, bleeding disorders, alcoholism, obesity; avoid in pregnancy (human teratogen); small risk of encephalopathy when combined with topiramate	Epilepsy, mania, anxiety	Nausea/vomiting, tremor, weight gain, alopecia, ↑ hepatic enzymes, neural tube defects (if used during pregnancy)
Topiramate	15 or 25 mg/d; ↑ by 15 mg weekly or 25 mg every 1-2 weeks	100 mg/d (at bedtime) or 50 mg BID; up to 200 mg/d may be used, if needed & tolerated	Kidney stones, kidney failure, angle closure glaucoma, pregnancy; small risk of encephalopathy when combined with valproate	Epilepsy, obesity, mania, anxiety, essential tremor, alcohol dependence	GI (nausea, anorexia); renal calculi; paresthesias; acute glaucoma; CNS (dizziness, tremor, sedation, cognitive impairment, depression); weight loss; metabolic acidosis
Gabapentin	300 mg/d & ↑ by 300 mg every 3-5 days, or start with 300 mg TID & ↑ weekly by 300 mg	1200-1500 mg/d (divided TID); up to 1800 mg/day may be used, if needed & tolerated	Kidney failure	Epilepsy, mania, anxiety, insomnia	Drowsiness, dizziness
Antidepressants:					
TCAs: Amitriptyline (or nortriptyline. Note: nortriptyline has no controlled trial evidence for efficacy)	10 mg/d (bedtime or 1 h before); ↑ by 10 mg every 1-2 weeks	20-40 mg/d (bedtime); up to 100-150 mg/d may be used, if needed & tolerated	Heart block, significant CV disease, urinary retention, uncontrolled glaucoma, prostate disease, mania	Insomnia, depression, anxiety, neuropathic pain, co-morbid tension-type headache	Weight gain, drowsiness, confusion, anticholinergic effects (dry mouth, constipation), ↓ seizure threshold, sexual dysfunction cardiovascular effects
SNRIs: Venlafaxine extended release	37.5 mg once daily for 1 week; ↑ weekly by 37.5 mg (may ↑ weekly by 75 mg)	150 mg/d (once daily)	Hypertension, kidney failure	Depression, anxiety	Nausea/vomiting, sexual dysfunction, drowsiness, dizziness, blurred vision
Antihypertensives: Beta-blockers:					
Propranolol	20-40 mg BID; ↑ by 20 mg BID every 1-2 weeks	80–160 mg/d (divided BID or LA form once daily)	Asthma, heart block, CHF, hypotension, bradycardia, Raynaud's, peripheral vascular disease, insulin-dependent diabetes, depression, sexual dysfunction	Hypertension, angina	Fatigue, reduced exercise tolerance, bradycardia, CHF, hypotension, bronchospasm, impotence, sleep disturbance
Nadolol	20-40 mg/d (morning); ↑ by 20-40 mg every 1-2 weeks	80–160 mg/d once daily	See Propranolol	See Propranolol	See Propranolol; may have fewer CNS side effects
Metoprolol	50 mg BID	100-200 mg/d (divided BID or SR form once daily)	See Propranolol	See Propranolol	See Propranolol

*Not all inclusive

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AV = atrioventricular; BID = twice daily; CHF = congestive heart failure; CHS = Canadian Headache Society; CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal; LA = long acting; MI = myocardial infarction; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; TCA = tricyclic antidepressant; TID = three times daily

Worthington I *et al. Can J Neurol Sci.* 2013;40(5 Suppl 3):S33-S62.

CHS Guidelines for Migraine Prophylaxis (2)

Recommended Dosages of Pharmacological Agents for Migraine Prophylaxis

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Calcium Channel Blockers:					
Flunarizine	5-10 mg/d (at bedtime); ↑ to 10 mg/d in 1-2 weeks (if start with 5 mg/d)	10 mg/d (at bedtime)	Depression, Parkinson's	Dizziness, vertigo	Weight gain, depression, drowsiness, extrapyramidal effects
Verapamil (not recommended for routine use because of low quality evidence for efficacy)	40 mg TID; ↑ to 80 mg TID over 1-2 weeks; SR: start with 160 mg/d; ↑ to 240 mg/d (divided BID) over 1-2 weeks	240 mg/d (divided TID; SR divided BID); doses > 480 mg/d not recommended	Constipation, hypotension, severe CHF, bradycardia, heart block, arrhythmias; avoid concomitant use with beta-blockers	Hypertension, angina	Constipation, peripheral edema, AV conduction disturbances
Antihypertensives: ACEIs/ARBs:					
Candesartan	8 mg/d, ↑ to 16 mg/d in 1 week (once daily)	16 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness
Lisinopril	10 mg/d (once daily)	20 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness, fatigue, non-productive cough, angioedema (rare)
Serotonin antagonists:					
Pizotifen (pizotyline)	0.5 mg at bedtime for 1 week; 0.5 mg BID for 1 week; 0.5 mg TID, ↑ up to 4 mg/d, if needed	1.5- 4 mg/d (1 mg BID is good target); full dose can be given at bedtime	Obesity	Insomnia	Drowsiness, weight gain (can be significant)
Vitamins/minerals/herbals:					
Riboflavin	400 mg/d (or 200 mg BID)	400 mg/d (once daily or divided BID)	None	None	Yellow discolouration of urine (benign)
Coenzyme Q10	100 mg TID	300 mg/d (100 mg TID to minimize GI adverse effects)	Hypotension	Hypertension	GI upset
Magnesium citrate	300 mg (elemental magnesium) BID	300 mg (elemental magnesium) BID	Kidney failure, diarrhea	Constipation	Diarrhea, GI upset
Butterbur (*Petasites*)	75 mg BID	75 mg BID	None	Allergic rhinitis	GI (burping)

*Not all inclusive

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AV = atrioventricular; BID = twice daily; CHF = congestive heart failure; CHS = Canadian Headache Society; CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal; LA = long acting; MI = myocardial infarction; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; TCA = tricyclic antidepressant; TID = three times daily

Worthington I *et al. Can J Neurol Sci.* 2013;40(5 Suppl 3):S33-S62.

Latin American Consensus on Guidelines for Chronic Migraine Treatment

Drug(s)	Comments
Topiramate	Use as migraine prophylaxis is based on class I studies with level A evidence
Sodium valproate and divalproate	Recommended in prophylaxis of episodic migraine, based on class I studies with level A evidence
Amitriptyline Gabapentin Pregabalin Tizanidine	Although studied for chronic daily headache by revealing efficacy (evidence levels I to III) were not specifically researched for migraine.
Type A botulinum toxin	Indicated for the prophylactic treatment of chronic migraine in patients aged 18 to 65 years
Non-pharmacologic measures/complementary therapies	Use is limited due lack of studies. One exception is acupuncture, which has shown promising results.

Medicines already proven as preventive for episodic migraine can be used alone or in combination, even without any evidence of their efficacy for chronic migraine

Giacomozzi AR *et al. Arq Neuropsiquiatr.* 2013;71(7):478-86.

EFNS Guideline on the Treatment of Migraine – Acute Therapies

Drug(s)	Comments
Analgesics	Drugs of first choice for mild or moderate attacks Intake of simple analgesics should be restricted to 15 days/month Intake of combined analgesics should be restricted to 10 days/month
Antiemetics	Recommended to treat nausea and potential vomiting and because it is assumed these drugs improve resorption of analgesics
Ergot alkaloids	Should be restricted to patients with very long migraine attacks or with regular occurrence Use must be limited to 10 days/month
Triptans	Efficacy of all triptans has been proven in large placebo-controlled trials and meta-analyses Use of triptans is restricted to maximum 9 days/month by IHS criteria Should not be taken during the aura
Opioids Tranquillizers	Should not be used in the acute treatment of migraine

EFNS = European Federation of Neurological Societies; IHS = International Headache Society

Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

EFNS Guideline on the Treatment of Migraine – Prophylactic Therapies

Prophylactic drug treatment of migraine should be considered and discussed with the patient when:

- Quality of life, business duties, or school attendance are severely impaired
- Frequency of attacks per month is ≥2
- Migraine attacks do not respond to acute drug treatment
- Frequent, very long, or uncomfortable auras occur

A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by ≥50% within 3 months

EFNS = European Federation of Neurological Societies

Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

EFNS Guideline on the Treatment of Migraine – Prophylactic Therapies

First-line recommendations

Substances	Daily dose (mg)	Level
Betablockers		
Metoprolol	50–200	A
Propranolol	40–240	A
Calcium channel blockers		
Flunarizine	5–10	A
Antiepileptic drugs		
Valproic acid	500–1800	A
Topiramate	25–100	A

Second-line recommendations

Substances	Daily dose (mg)	Level
Amitriptyline	50–150	B
Venlafaxine	75–150	B
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

Third-line recommendations

Substances	Daily dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200–1600 mg	C
Magnesium	24 mmol	C
Tanacetum parthenium	3 × 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4–12 mg	C

EFNS = European Federation of Neurological Societies; IHS = International Headache Society

Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

European Headache Federation Guideline – Acute Migraine

- Step one: symptomatic therapy with a simple analgesic
- Step two: specific therapy
  - Amlotriptan
  - Eletriptan
  - Frovatriptan
  - Naratriptan
  - Rizatriptan
  - Sumatriptan
  - Zolmitriptan
  - Ergotamine tartrate
- Triptans should be offered to all patients to fail step one if there are no contraindications
- Triptans should not be used regularly on >10 days/month

Steiner TJ *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

European Headache Federation Guideline – Prophylactic Management of Migraine

- Add prophylactic therapy when:
  - Attacks cause disability on ≥2 days/month **AND**
  - Optimized acute therapy does not prevent this **AND**
  - Patient is willing to take daily medication
- Effective drugs
  - β-blockers
  - Topiramate
  - Flunarizine
  - Sodium valproate
  - Amitriptyline
  - OnabotulinumtoxinA is currently not recommended for prophylaxis

Steiner TJ, Paemeleire K, Jensen R *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

European Headache Federation Guideline – Management of Tension-type Headache

- **Acute Intervention**
  - Use over-the-counter analgesics for episodic TTH occurring on ≤2 days/week
  - Episodic TTH on >2 days/week is an indication for prophylaxis in place of acute intervention
- **Prophylaxis**
  - Amitriptyline = drug of choice for frequent episodic or chronic TTH
  - Nortriptyline causes fewer side effects but has lower efficacy

TTH = tension-type headache

Steiner TJ, Paemeleire K, Jensen R *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

European Headache Federation Guideline – Management of Cluster Headache

- **Acute Intervention**
  - Sumatriptan 6 mg SC is the only proven highly effective acute treatment; use ≤ twice per day
  - 100% oxygen helps some people and may be used as needed
  - Analgesics, including opioids, have no place in treating cluster headaches
- **Prophylaxis**
  - Verapamil
  - Prednisolone
  - Lithium carbonate
  - Ergotamine tartrate
  - Methysergide

SC = subcutaneous

Steiner TJ, Paemeleire K, Jensen R *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

European Headache Federation Guideline – Management of Medication Overuse Headache

- Prevention (through education) is better than cure
- The only effective treatment of established MOH is withdrawal of the suspected medication(s)
- Once patient has gone through withdrawal and recovery, review and reassess underlying primary headache disorder
- Prevent relapse

MOH = medication overuse headache

Steiner TJ, Paemeleire K, Jensen R *et al. J Headache Pain*. 2007;8 Suppl 1:S3-47.

Barriers to Migraine Care

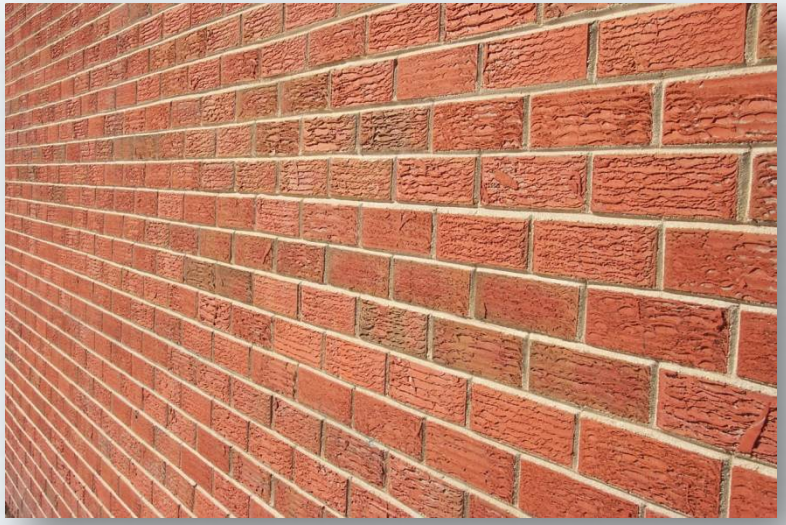
- **Overall barriers**
- **Adherence**
- **Strategies to improve adherence**

Overall Barrier to Migraine Care

Bigal M *et al. Headache.* 2009;49(7):1028-41.

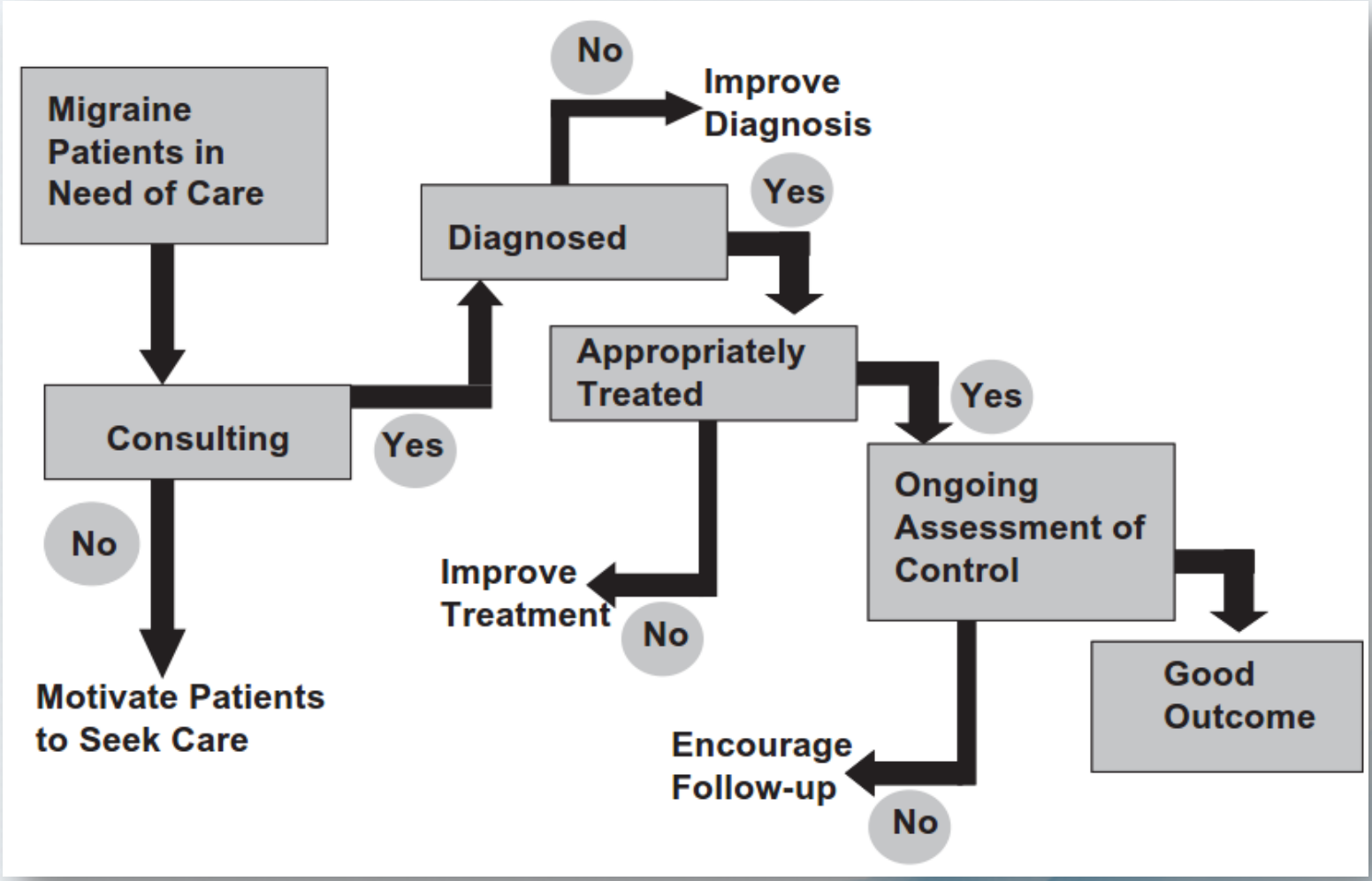
Barriers to Migraine Care

- Under-recognition and under-consultation by migraine sufferers
- Under-diagnosis and under-treatment by HCPs
- Lack of follow-up and treatment optimization
- Lack of preventative care



Bigal M *et al. Headache.* 2009;49(7):1028-41.

Barriers to Migraine Care



Bigal M *et al. Headache.* 2009;49(7):1028-41.

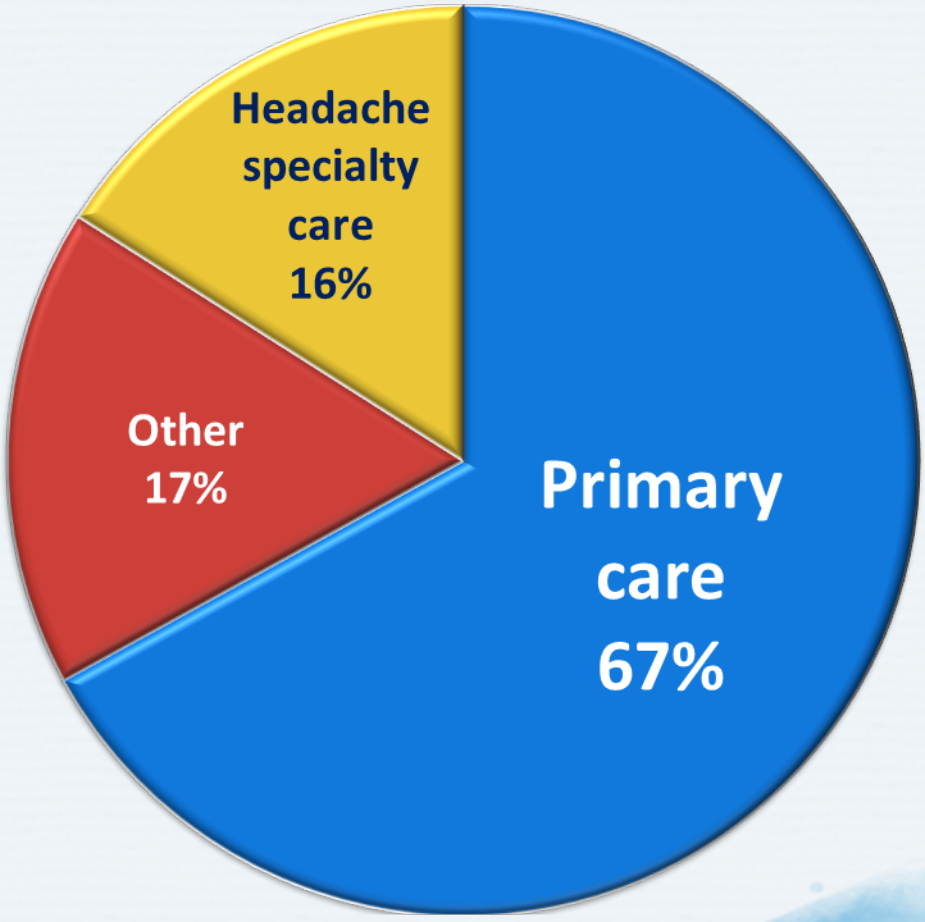
Barriers to Preventative Treatment of Migraine

- According to the 2005 American Migraine Prevention and Prevalence study:
  - 13% of migraineurs were taking preventative medication
  - 43.3% of migraineurs never used a preventative treatment
    - 19.3% met expert guideline criteria for receiving it
    - 13.1% met expert guideline criteria for having it considered
  - 25.5% of migraineurs had previously taken a preventative treatment
  - 18% of migraineurs were coincident users of preventative medication (*e.g.*, propanolol for hypertension)

AMPP = American Migraine Prevention and Prevalence Study; AMS-I = American Migraine Study-I; AMS-II = American Migraine Study-II; ICHD = International Classification of Headache Disorders.

Bigal M *et al. Headache.* 2009;49(7):1028-41.

Where Do Migraine Sufferers Seek Medical Care?



Lipton RB *et al. Headache.* 1998;38:87-96.

Medical System Barriers to Migraine Care

- Migraine is often managed in the primary care setting
  - Time is lacking
  - Not enough time to evaluate a patient and develop an appropriate treatment plan
- Resources are also lacking in specialty care
  - Few neurologists
  - Lack of recognition of burden of headache and migraine as a neurological disease
  - Lack of migraine awareness

Bigal M *et al. Headache.* 2009;49(7):1028-41.

Adherence

- **Prevalence of Non-adherence**
- **Strategies to promote adherence**

Importance of Adherence to Migraine Medication

Non-adherence may lead to:

- Overuse of over-the-counter drugs
- Possible progression to chronic headache
- Possible drug interactions
- Potential for increased emergency room visits

Katić BJ, Krause SJ, Tepper SJ *et al. Headache*. 2010;50(1):117.

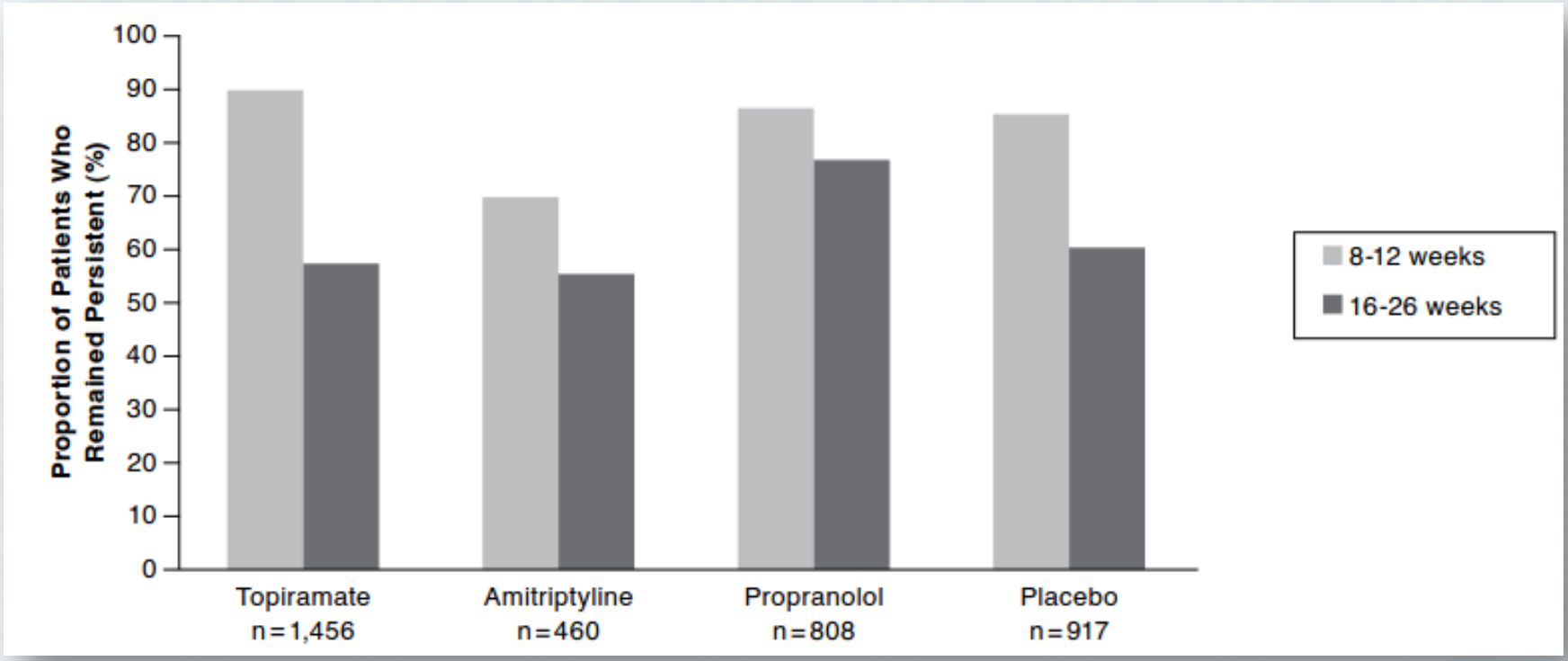
Scope of Lack of Adherence to Migraine Medication

- Most studies measure prophylactic use of drugs
- 62% of migraineurs given a prescription; only 34% continued to use the medication at the time of the survey
- Studies have shown 6-11% of patients don't fill prescriptions
- Many patients delay use of prescription medications at migraine onset
- Triptans are particularly underutilized
  - 11% of 1160 patients experiencing severe headaches did not fill a previously issued prescription for a medication
  - Triptan sales are stable over time
    - For each patient starting a triptan, another patient discontinues use

Katić BJ, Krause SJ, Tepper SJ *et al. Headache*. 2010;50(1):117.

Persistence with Migraine Medications

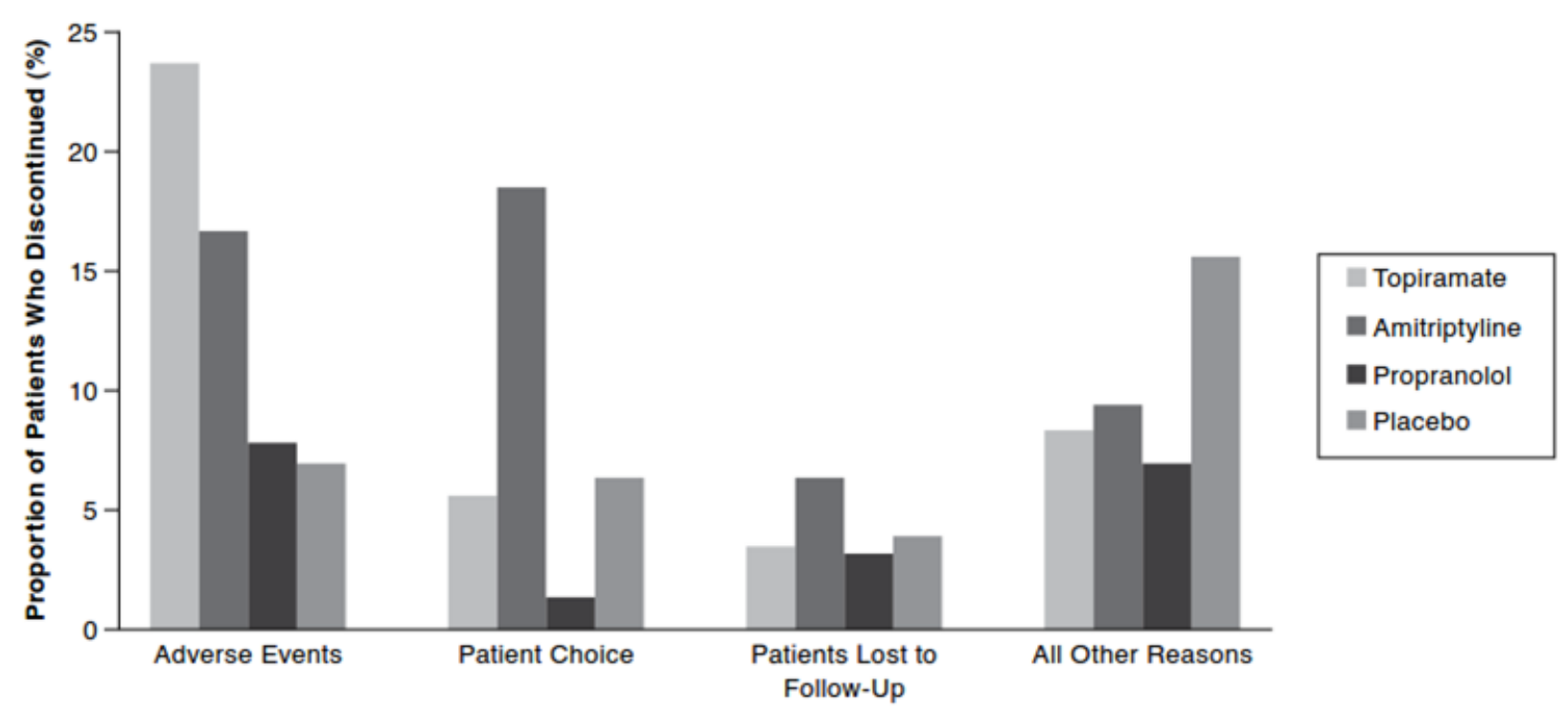
Combined Weighted Persistence Rates from Randomized Controlled Trials



Hepp Z, Bloudek LM, Varon SF. *J Manag Care Pharm.* 2014;20(1):22-33.

Discontinuation of Migraine Medications by Cause

Weighted Discontinuation Rate by Cause



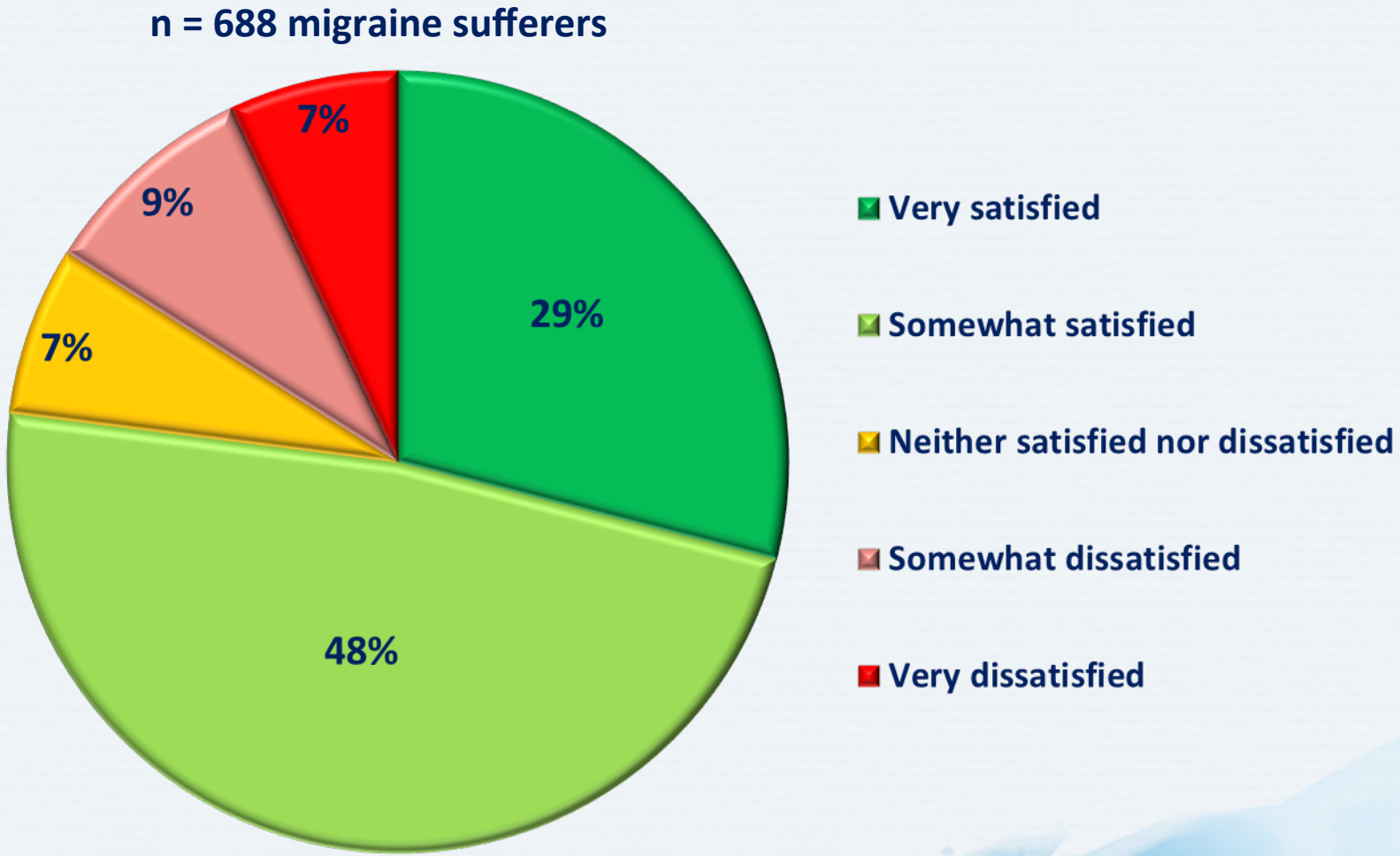
Hepp Z, Bloudek LM, Varon SF. *J Manag Care Pharm.* 2014;20(1):22-33.

Importance of Understanding Patient Preferences in Treating Migraine

- Failure to understand patient preferences may reduce adherence and discourage patients from continuing treatment
- A thorough understanding of each patient's individual expectations for migraine treatment is needed
- Understanding patients' needs improves chances for successful migraine management
- Permits selection of most suitable migraine therapy

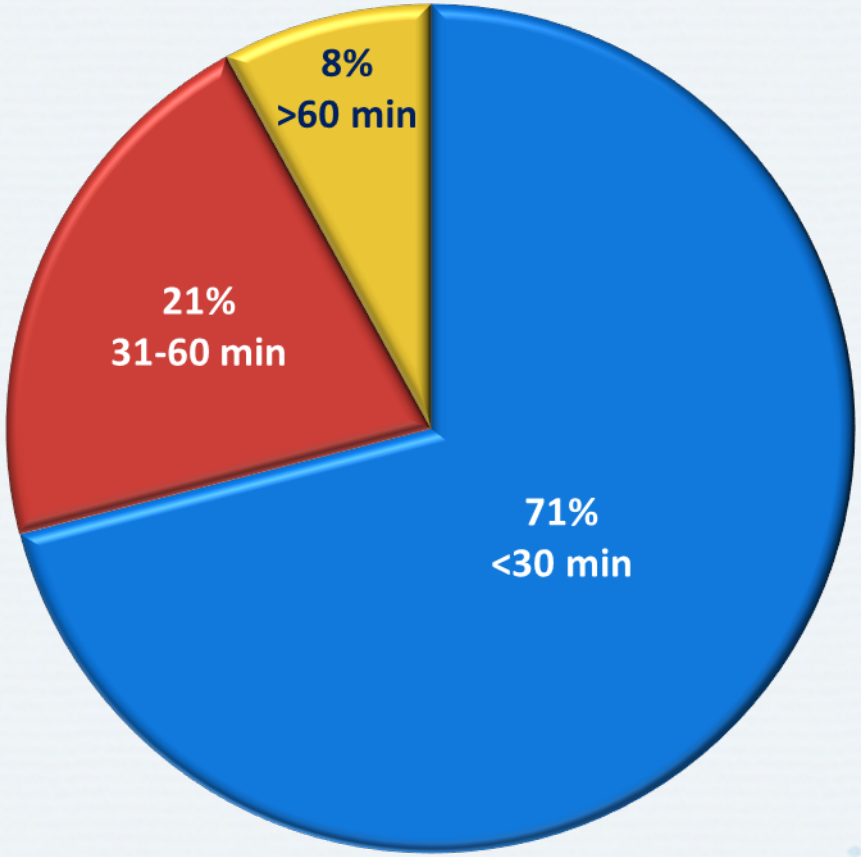
Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Are Migraine Sufferers Satisfied with their Acute Therapy?



Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

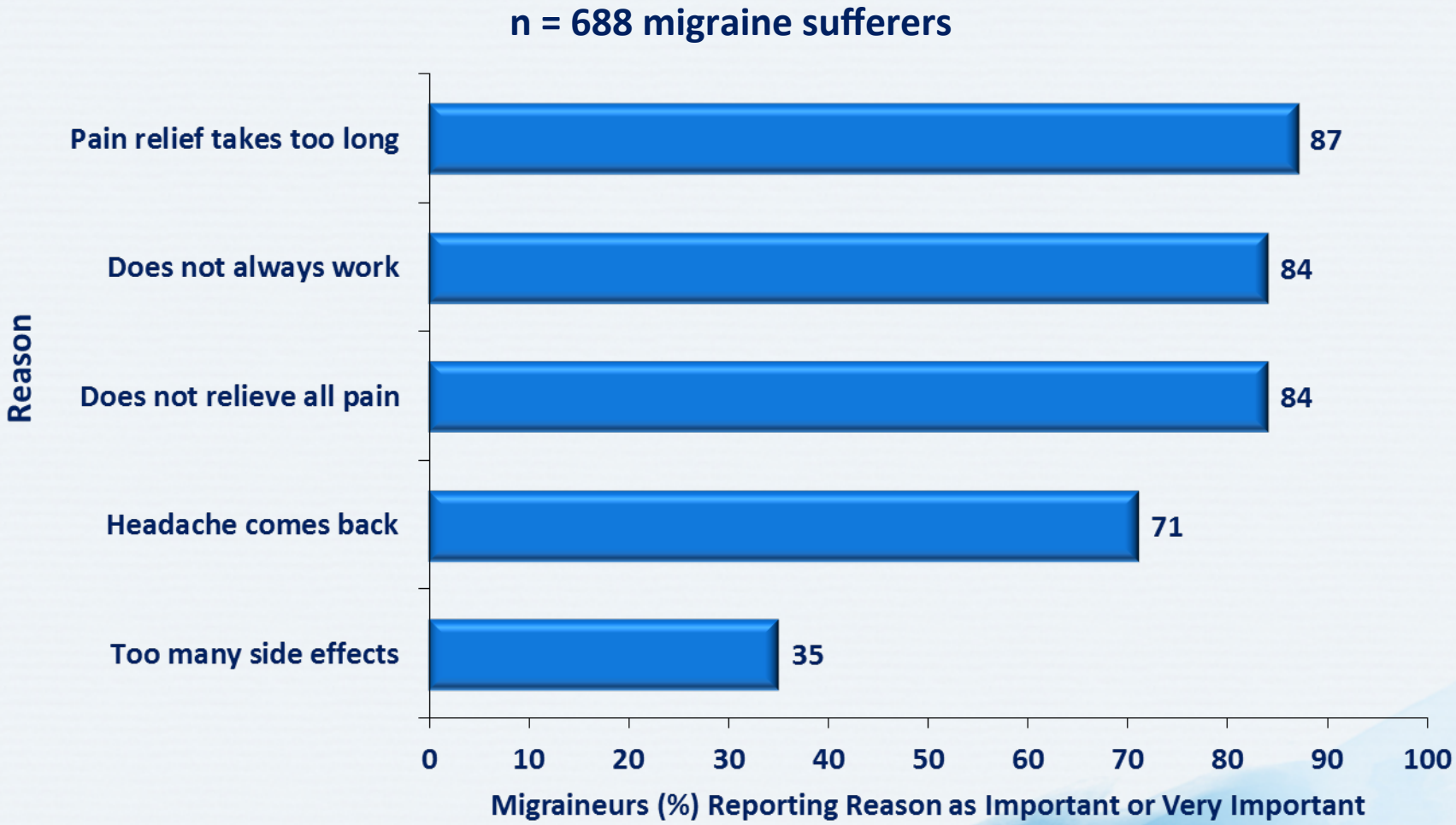
How Long Should a Rapidly Acting Tablet Take to Satisfactorily Relieve Pain?



n = 688 migraine sufferers

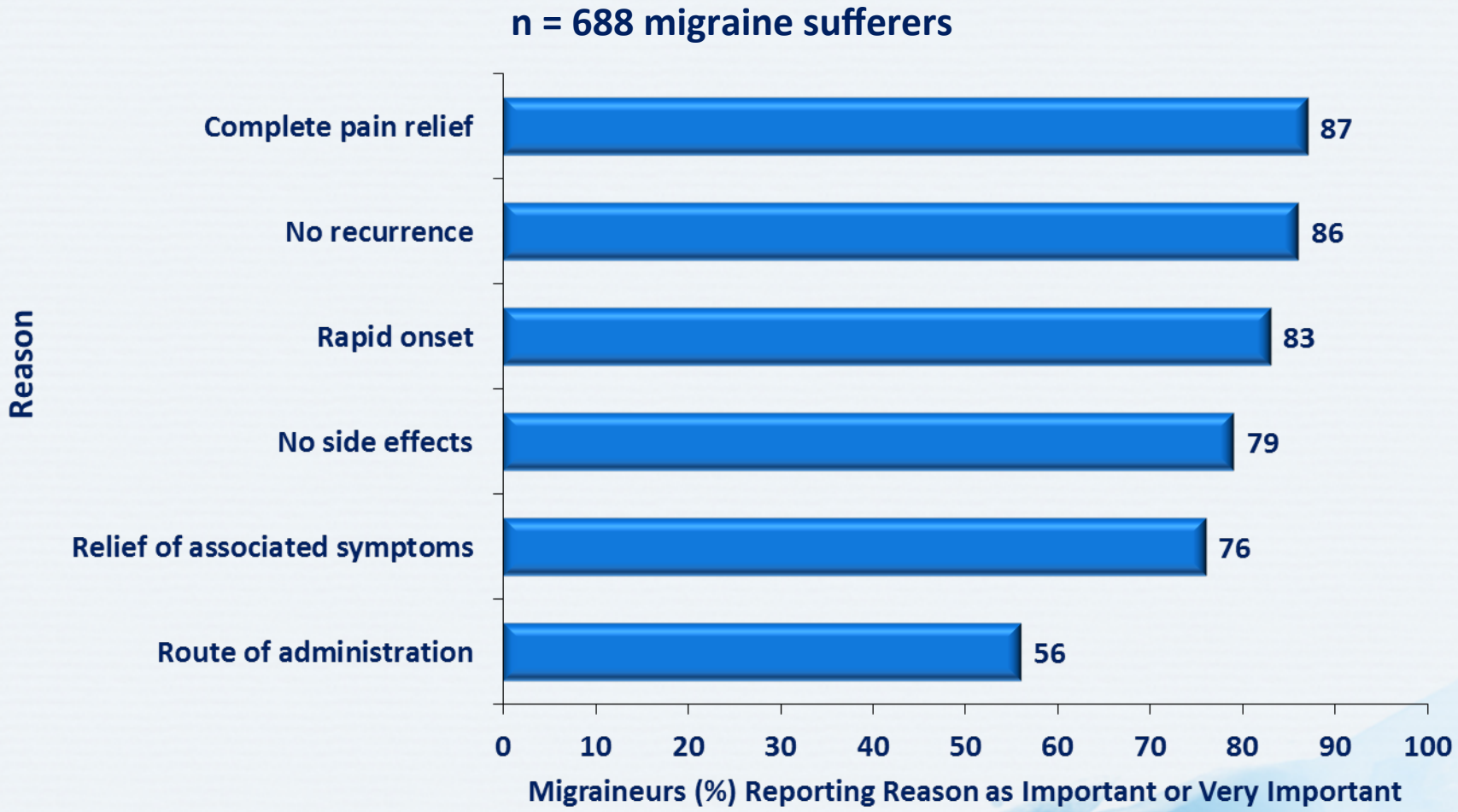
Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Reasons for Dissatisfaction with Acute Medications for Migraine



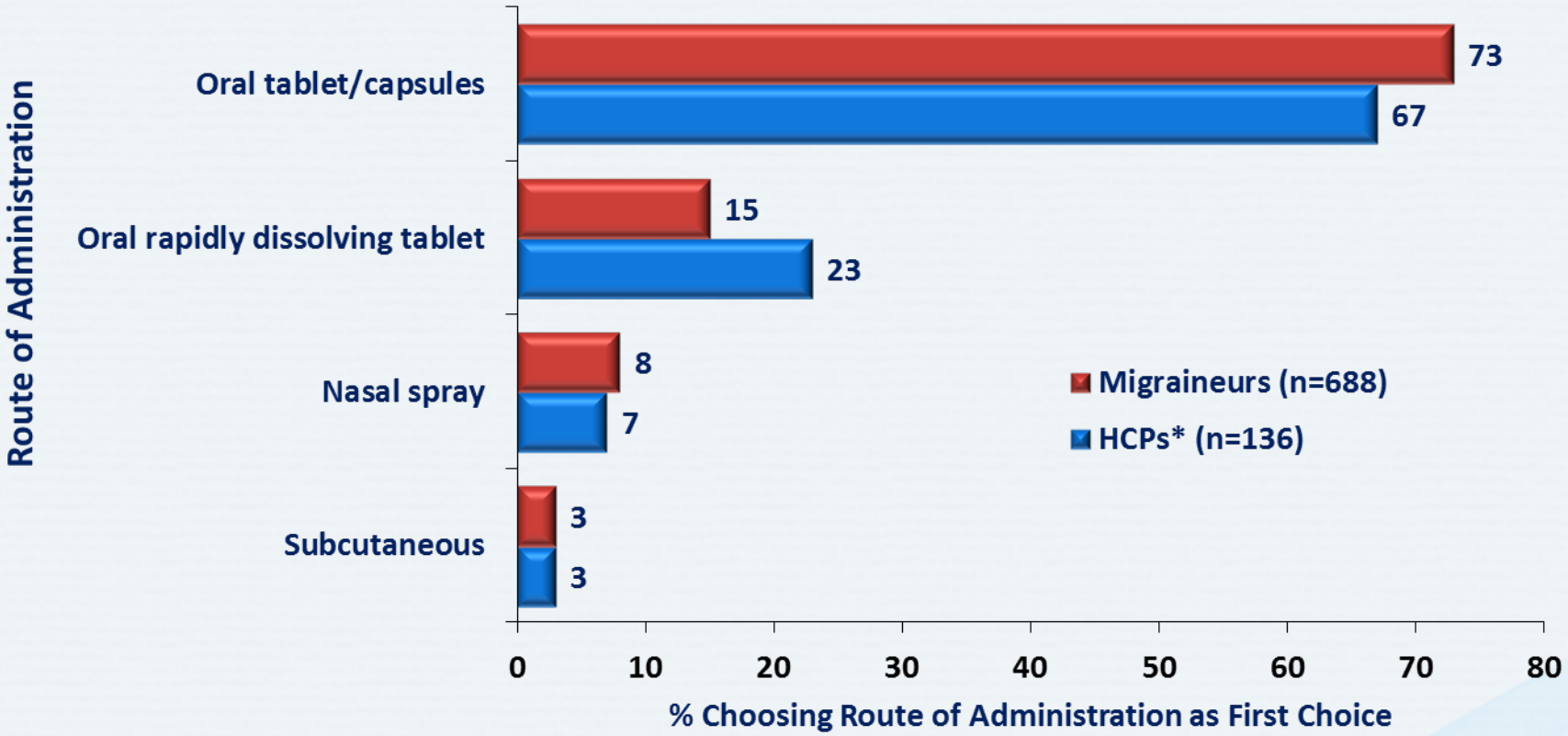
Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Important or Very Important Attributes of Acute Medications for Migraine



Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Preferred Route of Administration of Acute Migraine Medication

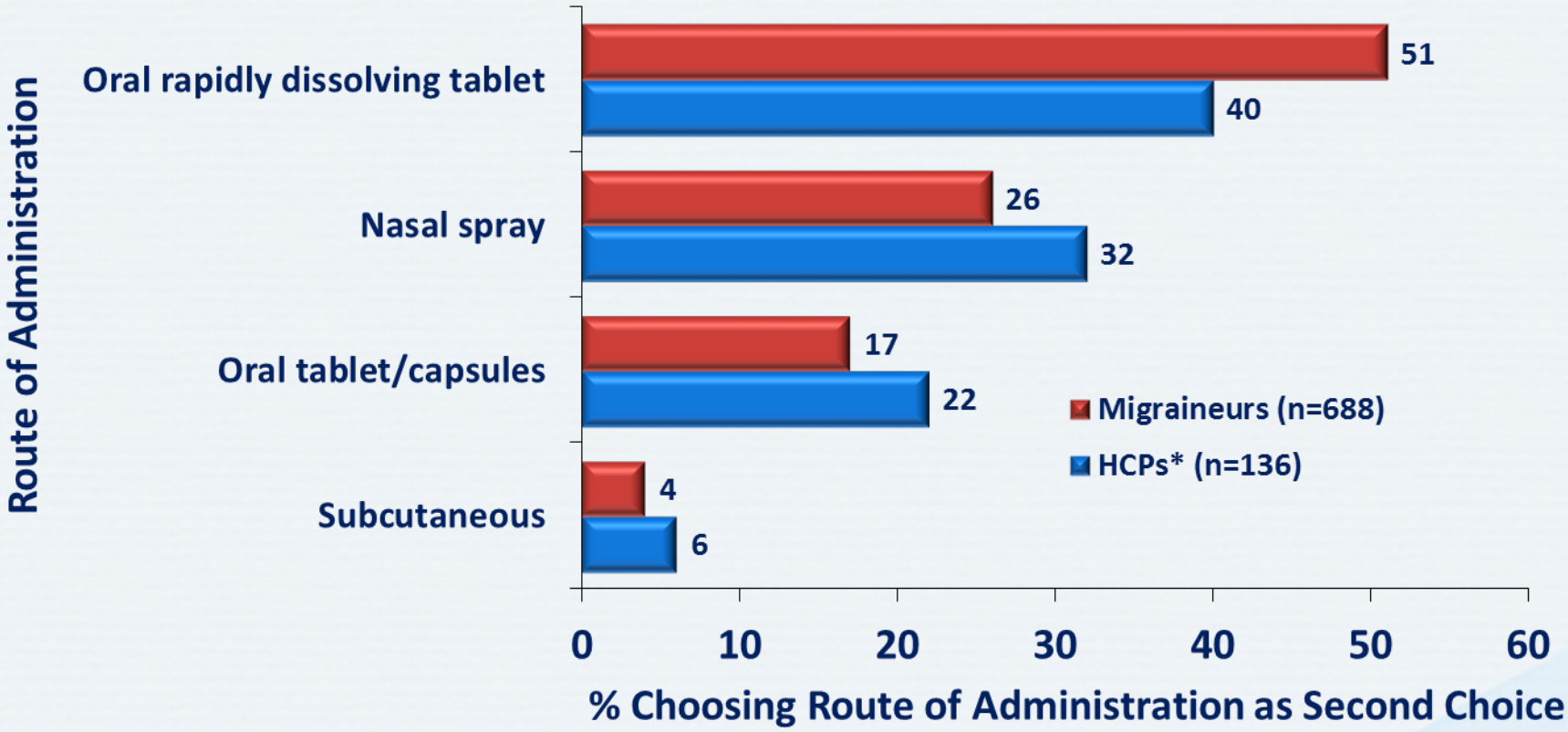


*85 physicians Included neurologists (68%), family/general practitioners (11%), internists (6%), and other physicians (14%). Non-physicians included pharmacists, doctors of pharmacy, pharmacologists, psychologists, other mental health professionals, and nurses.

HCP = health care providers

Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Second Choice of Route of Administration of Acute Migraine Medication

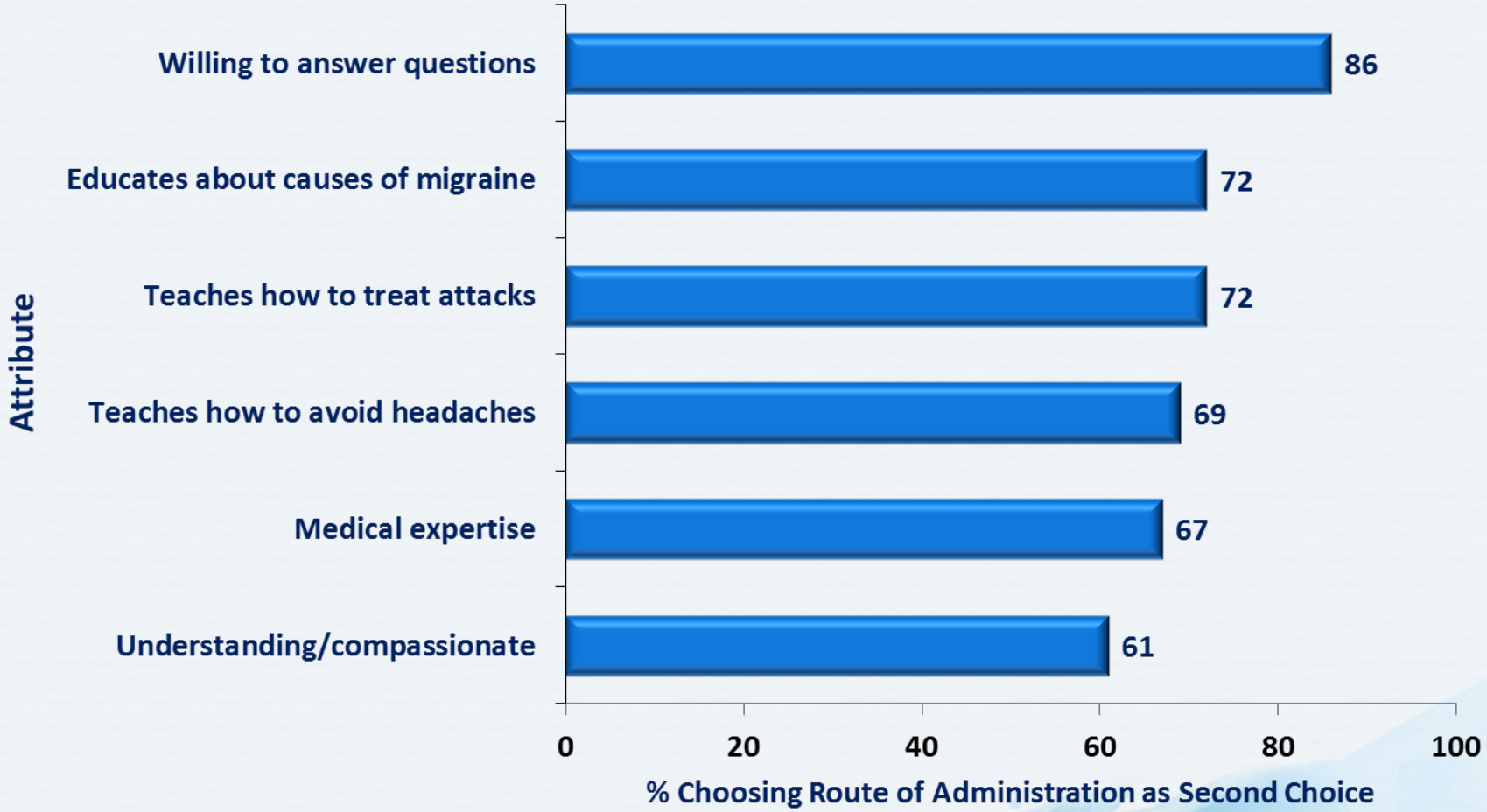


*85 physicians Included neurologists (68%), family/general practitioners (11%), internists (6%), and other physicians (14%). Non-physicians included pharmacists, doctors of pharmacy, pharmacologists, psychologists, other mental health professionals, and nurses.

HCP = health care providers

Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Physician Attributes Rated as Very Important or Important by Migraine Sufferers



HCP = health care providers

Lipton RB, Stewart WF. *Headache.* 1999;29(suppl 2):S20-S26.

Patient Barriers to Early Treatment of Migraine

- **Migraine sufferers often delay taking their acute migraine medications**

1. Is it a migraine?

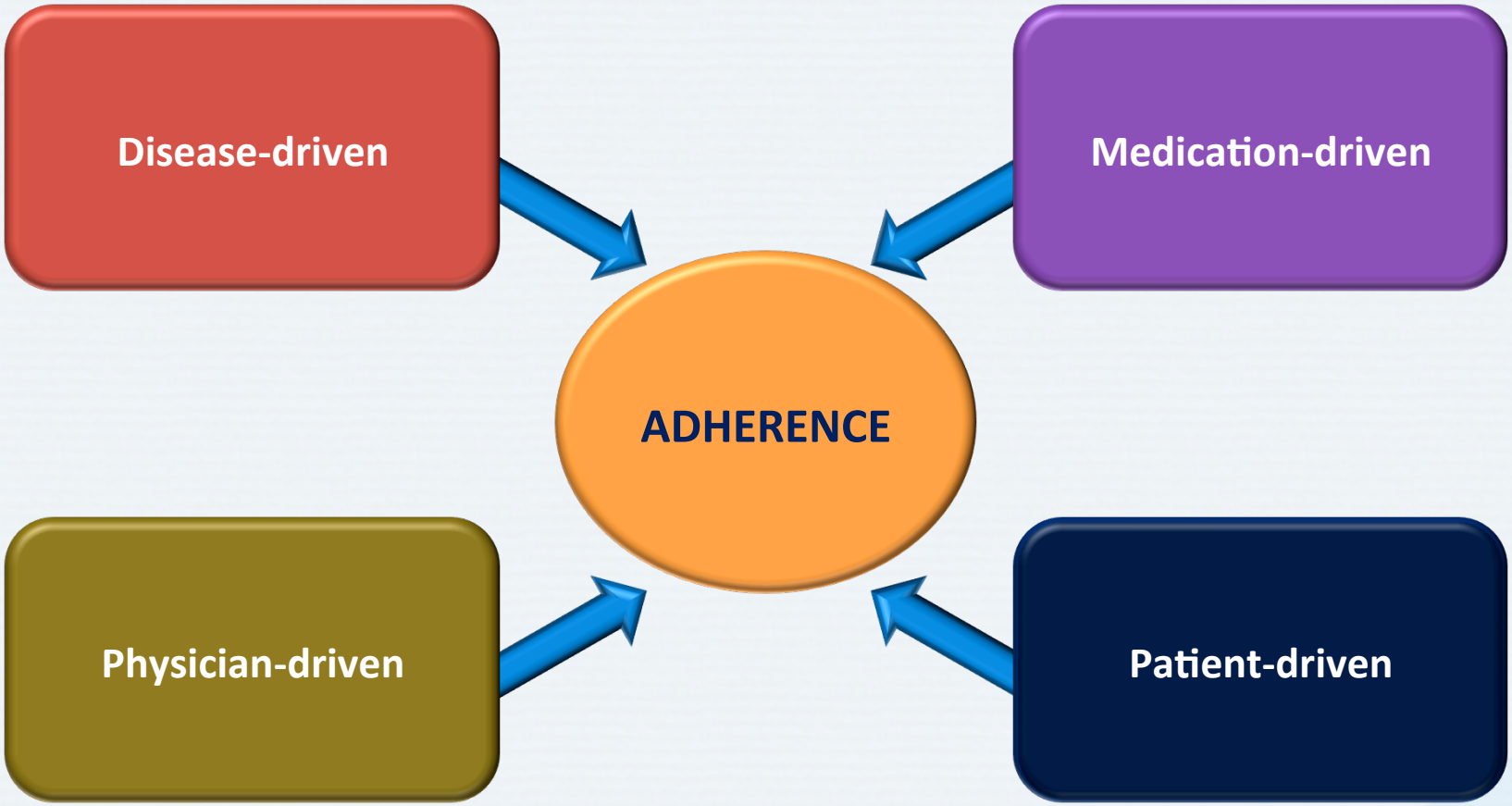
2. Weigh factors (*e.g.*, degree of pain, concerns about side effects)*

Decision whether or not to take medication

About of half of migraine sufferers often avoid or delay taking their migraine medications when they start to experience a migraine attack
→Important to teach patients how to differentiate migraines from other headaches.

*Many patients only want to take medications if it is a severe attack
Bigal M *et al. Headache.* 2009;49(7):1028-41.

Barriers to Migraine Care – Adherence Issues



*Many patients only want to take medications if it is a severe attack

Bigal M *et al. Headache.* 2009;49(7):1028-41.

Issues Related to Lack of Persistence with Migraine Treatment

Determinant	Relevance	Potential modifiable factors (hypotheses)
Disease's driven	This determinant works as an "umbrella" factor. If the disease is seen as trivial, patients may be less motivated to use meds. Accordingly, understanding this component will drive all the other determinants.	Neutralizing concepts such as: (1) Migraine is not lethal. (2) Migraine is another annoying part of life that I have to deal with. (3) Migraine has nothing to do with the brain. (4) Migraine may be treated with OTCs and analgesics (see link with medication overuse project).
Medication's driven	Understanding factors associated with satisfaction/dissatisfaction after using specific meds over the long haul increase maintenance of therapy strategies.	Why are the determinants of low maintenance to therapy? (1) Adverse events? (2) Formulary restrictions? (3) Fear (perception of safety)?
Physician's driven	Some doctors are more efficient than others in engaging patients. Why?	(1) Do they request follow-up visits? (2) Do they explain more about the disease? (3) Are they less focused on rare side effects?
Patient's driven	What factors are associated with the decision making process about using meds? And being actively engaged with the plan?	(1) Lack of disease-specific knowledge may be associated with poor adherence and MDs have little time to educate patients. (2) Comorbidities (anxiety, depression) may interfere in adherence. (3) Unrealistic expectations may impact adherence.

Bigal M *et al. Headache.* 2009;49(7):1028-41.

Predictors of Preventive Migraine Medication Adherence in African American and Caucasian Headache Patients

Predictor variable	OR	95% CI for OR	*P*
Age (years)	1.00	0.96-1.05	.89
Years of education	0.99	0.80-1.24	.98
Being female	0.29	0.04-2.39	.25
Being African American	0.49	0.19-1.26	.14
Headache days per month	1.02	0.96-1.08	.63
Headache episode severity	2.02	0.56-7.28	.28
Headache management self-efficacy	1.02	1.01-1.05	.03
Being diagnosed with MDD	0.34	0.13-0.87	.03
Race × headache episode severity	9.87	0.60-161.54	.11
Race × headache days per month	1.09	0.95-1.25	.25
Race × major depression diagnosis	0.35	0.05-2.91	.36

- **Adherence did not differ between African American and Caucasian patients**
- **Patients who reported greater headache management self-efficacy were *more likely to adhere to medication***
- **Patients who reported MDD were *less likely to adhere to medication***

Heckman BD, Ellis G. *Headache*. 2011;51(4):520-32.

Medication Regimen Complexity Does Not Influence Adherence to Migraine Medications

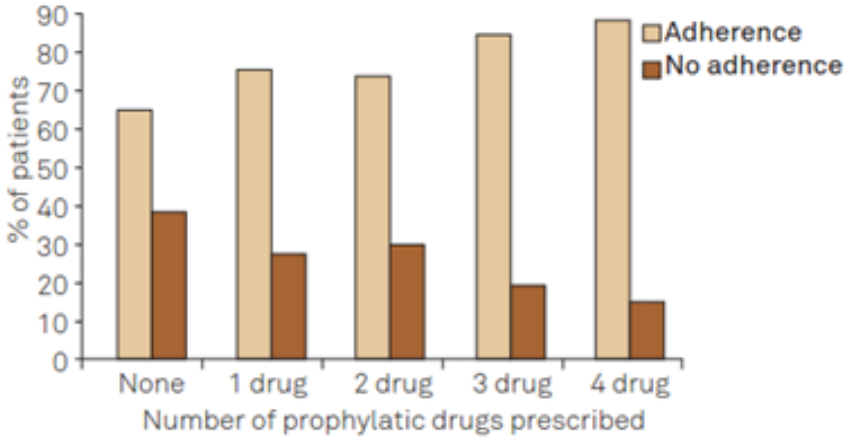


Figure. Correlation between adherence and number of prophylactic medication prescribed.

Table. Comparison of adherence to different treatment strategies.

Treatment	Adherence (%)	Treatments comparison
1 drug 2 drugs	73.7 71.8	ns[1]
1 drug 3 drugs	73.7 82.6	ns
1 drug 4 drugs	73.7 86.3	ns
2 drugs 3 drugs	71.8 82.6	p>0.05
2 drugs 4 drugs	71.8 86.3	p>0.05
3 drugs 4 drugs	82.6 86.3	ns

[1]Not statistically significant: p>0.05.

There is no difference in adherence to monotherapy or polytherapy (one to four drugs) for the prophylaxis of migraine

Dozza AL, Krymchantowski AV. *Arq Neuropsiquiatr.* 2013;71(3):171-3.

Assessing Adherence to Migraine Medication

- Pharmacy claims data
  - Prescriptions and refills
  - Pill counts
  - Persistency
- Clinic-based studies
  - Medical records
  - Clinical data
  - Matched physician-patient surveys
- Patient self-report
  - Validated patient questionnaires
  - Migraine diaries
  - Qualitative, anecdotal data

Katić BJ, Krause SJ, Tepper SJ *et al. Headache*. 2010;50(1):117.

Reasons for Non-adherence to Migraine Medications

- Adherence in patients with chronic health conditions is usually ≤80%
- Non-adherence has a huge economic impact
- Benefits of preventive headache agents are largely dependent on consistent adherence
- Why are migraine sufferers not adherent to medications?
  - Patients who suffer migraines may find it difficult to adhere to headache medications whose benefits do not outweigh adherence-related challenges
    - Cost of drugs, negative side effects, perceived inefficacy of drugs
  - Headaches can be relatively intermittent (vs. other chronic illnesses), which may predispose some headache patients to poorer adherence

Heckman BD, Ellis G. *Headache*. 2011;51(4):520-32.

Strategies to Promote Adherence to Migraine Treatments

Determinant	Relevance	Potential actions
Disease's driven	This determinant works as an "umbrella" factor. If the disease is seen as trivial, patients may be less motivated to use meds. Accordingly, understanding this component will drive all the other determinants.	Awareness campaigns focusing on: (1) Nobody should live with pain. (2) There are consequences of poor management (eg, migraine progression). (3) Migraine is a disorder of the brain. (4a) There are medications that target the very biology of migraine. (4b) Medication overuse is a consequence of migraine mismanagement.
Medication's driven	Understanding factors associated with satisfaction/dissatisfaction after using specific meds over the long haul increase maintenance of therapy strategies.	Based on findings, to build awareness campaigns accounting for the fear factor, limited formulary and limited knowledge of disease.
Physician's driven	Some doctors are more efficient than others in engaging patients. Why?	(1) Education activities that focus on health provider's actions that are associated with satisfaction and adherence.
Patient's driven	What factors are associated with the decision making process about using meds? And being actively engaged with the plan?	Patient-centered education activities (tapes, web-based, short education activities) may increase adherence in a cost-effective way.

Bigal M *et al. Headache.* 2009;49(7):1028-41.

Future Treatment Options

CGRP Antagonists ("Gepants") for Migraine

- Calcitonin gene-related peptide (CGRP) plays an integral role in the pathophysiology of migraine
  - Jugular CGRP levels are increased during migraine attacks
  - Intravenous CGRP administration induces migraine-like headache in most migraineurs
- Non-peptide CGRP antagonists now available as monoclonal antibodies
  - Target a specific migraine mechanism
    - Target CGRP pathway with exquisite specificity and long half-lives
- No vasoconstrictor properties
- Adverse effect profile similar to placebo

Gepants are the most prolific class with multiple agents under development for both acute and preventative treatment of migraine

Bigal ME, Walter S. *CNS Drugs*. 2014;28:389-99; Magis D, Schoenen J. *Curr Opin Neurol.* 2011;24:203-10; Tso AR, Goadsby PJ. *Curr Treat Options Neurol.* 2014;16:318.

Ditans for Acute Migraine Therapy

- Ditans are serotonin 5-HT_{1F} agonists
- Triptans are potent serotonin 5-$HT_{1B/1D}$ receptor antagonists
  - Can cause vasoconstriction via 5-HT_{1B} receptors
- Activation of 5-HT_{1F} receptors decreases c-Fos expression (marker of neuronal activation) in trigeminal nucleus caudalis without vascular effects
- Ditans lack the contraindications that limit triptan use
- Lasmiditan (vs. placebo) provides a better 2-hour headache response in migraineurs
  - Separation from placebo can start as early as 30 minutes
  - Common side effects of lasmiditan are dizziness, paresthesias, and sensation of limb heaviness
  - Does not cause the chest symptoms of triptans

Magis D, Schoenen J. *Curr Opin Neurol.* 2011;24:203-10; Tso AR, Goadsby PJ. *Curr Treat Options Neurol.* 2014;16:318.

Literature Cited

Allergan. (2015). BOTOX® Prescribing Information - botox_pi.pdf. Retrieved June 18, 2015, from http://www.allergan.com/assets/pdf/botox_pi.pdf

American Headache Society. (2004). Brainstorm. Retrieved June 18, 2015, from http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf

Arulmozhi, D. K., Veeranjaneyulu, A., & Bodhankar, S. L. (2005). Migraine: current concepts and emerging therapies. *Vascular Pharmacology*, *43*(3), 176–187. http://doi.org/10.1016/j.vph.2005.07.001

Aukerman, G., Knutson, D., Miser, W. F., & Department of Family Medicine, Ohio State University College of Medicine and Public Health, Columbus, Ohio. (2002). Management of the acute migraine headache. *American Family Physician*, *66*(11), 2123–2130.

Belvís, R., Pagonabarraga, J., & Kulisevsky, J. (2009). Individual triptan selection in migraine attack therapy. *Recent Patents on CNS Drug Discovery*, *4*(1), 70–81.

Bigal, M., Krymchantowski, A. V., & Lipton, R. B. (2009). Barriers to satisfactory migraine outcomes. What have we learned, where do we stand? *Headache*, *49*(7), 1028–1041. http://doi.org/10.1111/j.1526-4610.2009.01410.x

Literature Cited *(Continued)*

Blumenfeld, A., Ashkenazi, A., Napchan, U., Bender, S. D., Klein, B. C., Berliner, R., … Robbins, M. S. (2013). Expert consensus recommendations for the performance of peripheral nerve blocks for headaches--a narrative review. *Headache*, *53*(3), 437–446. http://doi.org/10.1111/head.12053

Blumenfeld, A., & Robbins, M. (n.d.). Peripheral Nerve Blocks. Retrieved June 18, 2015, from http://www.americanheadachesociety.org/assets/1/7/Andrew_Blumenfeld_and_Matthew_Robbins_-_Peripheral_Nerve_Blocks.pdf

Blumenfeld, A., Silberstein, S. D., Dodick, D. W., Aurora, S. K., Turkel, C. C., & Binder, W. J. (2010). Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache*, *50*(9), 1406–1418. http://doi.org/10.1111/j.1526-4610.2010.01766.x

Bruce, K. (2010). *Guide to Pain Management in Low-Resource Settings*. Seattle, WA: International Association for the Study of Pain.

Chawla, J. (n.d.). Migraine Headache: Practice Essentials, Background, Pathophysiology. Retrieved June 18, 2015, from http://emedicine.medscape.com/article/1142556-overview

Clemett, D., & Goa, K. L. (2000). Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs*, *59*(4), 957–980.

Literature Cited *(Continued 2)*

Demaagd, G. (2008). The pharmacological management of migraine, part 1: overview and abortive therapy. *P & T: A Peer-Reviewed Journal for Formulary Management*, *33*(7), 404–416.

Dodick, D. W., Turkel, C. C., DeGryse, R. E., Aurora, S. K., Silberstein, S. D., Lipton, R. B., … PREEMPT Chronic Migraine Study Group. (2010). OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*, *50*(6), 921–936. http://doi.org/10.1111/j.1526-4610.2010.01678.x

Durham, P. L., & Cady, R. (2011). Insights into the mechanism of onabotulinumtoxinA in chronic migraine. *Headache*, *51*(10), 1573–1577. http://doi.org/10.1111/j.1526-4610.2011.02022.x

Evers, S., Afra, J., Frese, A., Goadsby, P. J., Linde, M., May, A., … European Federation of Neurological Societies. (2009). EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, *16*(9), 968–981. http://doi.org/10.1111/j.1468-1331.2009.02748.x

Ferrari, M. D., Roon, K. I., Lipton, R. B., & Goadsby, P. J. (2001). Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet (London, England)*, *358*(9294), 1668–1675. http://doi.org/10.1016/S0140-6736(01)06711-3

Literature Cited *(Continued 3)*

Fumal, A., & Schoenen, J. (2008). Current migraine management - patient acceptability and future approaches. *Neuropsychiatric Disease and Treatment*, *4*(6), 1043–1057.

Gallagher, R. M., Mueller, L. L., & Freitag, F. G. (2002). Divalproex sodium in the treatment of migraine and cluster headaches. *The Journal of the American Osteopathic Association*, *102*(2), 92–94.

Garza, I., & Swanson, J. W. (2006a). Prophylaxis of migraine. *Neuropsychiatric Disease and Treatment*, *2*(3), 281–291.

Garza, I., & Swanson, J. W. (2006b). Prophylaxis of migraine. *Neuropsychiatric Disease and Treatment*, *2*(3), 281–291.

Giacomozzi, A. R. E., Vindas, A. P., Silva, A. A. da, Bordini, C. A., Buonanotte, C. F., Roesler, C. A. de P., … Filho, P. F. M. (2013). Latin American consensus on guidelines for chronic migraine treatment. *Arquivos De Neuro-Psiquiatria*, *71*(7), 478–486. http://doi.org/10.1590/0004-282X20130066

Goadsby, P. J., Lipton, R. B., & Ferrari, M. D. (2002). Migraine--current understanding and treatment. *The New England Journal of Medicine*, *346*(4), 257–270. http://doi.org/10.1056/NEJMra010917

Grosser, T. (2010). *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (12th ed). New York, NY: McGraw-Hill.

Literature Cited *(Continued 4)*

Guyuron, B., Kriegler, J. S., Davis, J., & Amini, S. B. (2011). Five-year outcome of surgical treatment of migraine headaches. *Plastic and Reconstructive Surgery*, *127*(2), 603–608. http://doi.org/10.1097/PRS.0b013e3181fed456

Guyuron, B., Reed, D., Kriegler, J. S., Davis, J., Pashmini, N., & Amini, S. (2009). A placebo-controlled surgical trial of the treatment of migraine headaches. *Plastic and Reconstructive Surgery*, *124*(2), 461–468. http://doi.org/10.1097/PRS.0b013e3181adcf6a

Hepp, Z., Bloudek, L. M., & Varon, S. F. (2014). Systematic review of migraine prophylaxis adherence and persistence. *Journal of Managed Care Pharmacy: JMCP*, *20*(1), 22–33.

Holland, S., Silberstein, S. D., Freitag, F., Dodick, D. W., Argoff, C., Ashman, E., & Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. (2012). 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*, *78*(17), 1346–1353. http://doi.org/10.1212/WNL.0b013e3182535d0c

John, P. J., Sharma, N., Sharma, C. M., & Kankane, A. (2007). Effectiveness of yoga therapy in the treatment of migraine without aura: a randomized controlled trial. *Headache*, *47*(5), 654–661. http://doi.org/10.1111/j.1526-4610.2007.00789.x

Literature Cited *(Continued 5)*

Katić, B. J., Krause, S. J., Tepper, S. J., Hu, H. X., & Bigal, M. E. (2010). Adherence to acute migraine medication: what does it mean, why does it matter? *Headache*, *50*(1), 117–129. http://doi.org/10.1111/j.1526-4610.2009.01535.x

Linde, K., Streng, A., Jürgens, S., Hoppe, A., Brinkhaus, B., Witt, C., … Melchart, D. (2005). Acupuncture for patients with migraine: a randomized controlled trial. *JAMA*, *293*(17), 2118–2125. http://doi.org/10.1001/jama.293.17.2118

Lipton, R. B., Cutrer, F. M., Goadsby, P. J., Ferrari, M. D., Dodick, D. W., McCrory, D., … Williams, P. (2005). How treatment priorities influence triptan preferences in clinical practice: perspectives of migraine sufferers, neurologists, and primary care physicians. *Current Medical Research and Opinion*, *21*(3), 413–424. http://doi.org/10.1185/030079905X36387

Lipton, R. B., & Stewart, W. F. (1999). Acute migraine therapy: do doctors understand what patients with migraine want from therapy? *Headache*, *39*(2), S20.

Lipton, R. B., Stewart, W. F., & Simon, D. (1998). Medical consultation for migraine: results from the American Migraine Study. *Headache*, *38*(2), 87–96.

Mathew, N. T., Rapoport, A., Saper, J., Magnus, L., Klapper, J., Ramadan, N., … Tepper, S. (2001). Efficacy of gabapentin in migraine prophylaxis. *Headache*, *41*(2), 119–128.

Mattia, A., & Coluzzi, F. (2009). What anesthesiologists should know about paracetamol (acetaminophen). *Minerva Anestesiologica*, *75*(11), 644–653.

Literature Cited *(Continued 6)*

Mauskop, A. (2012). Nonmedication, alternative, and complementary treatments for migraine. *Continuum (Minneapolis, Minn.)*, *18*(4), 796–806. http://doi.org/10.1212/01.CON.0000418643.24408.40

Migraine Clinics | The Migraine Trust. (n.d.). Retrieved June 18, 2015, from http://www.migrainetrust.org/factsheet-migraine-clinics-10783

Parsekyan, D. (2000). Migraine prophylaxis in adult patients. *The Western Journal of Medicine*, *173*(5), 341–345.

Pharmacological Management of Acute Attacks - gl0087.pdf. (n.d.). Retrieved June 18, 2015, from http://tools.aan.com/professionals/practice/pdfs/gl0087.pdf

Scholz, J., & Woolf, C. J. (2002). Can we conquer pain? *Nature Neuroscience*, *5 Suppl*, 1062–1067. http://doi.org/10.1038/nn942

Shank, R. P., Gardocki, J. F., Streeter, A. J., & Maryanoff, B. E. (2000). An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*, *41 Suppl 1*, S3–9.

Silberstein, S. (1998). *Headache in Clinical Practice*. Oxford, England: Isis Medical Media.

Silberstein, S. D. (2000). Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, *55*(6), 754–762.

Literature Cited *(Continued 7)*

Silberstein, S. D., Holland, S., Freitag, F., Dodick, D. W., Argoff, C., Ashman, E., & Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. (2012). 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*, *78*(17), 1337–1345. http://doi.org/10.1212/WNL.0b013e3182535d20

Steiner, T. J., Paemeleire, K., Jensen, R., Valade, D., Savi, L., Lainez, M. J. A., … World Health Organization. (2007). European principles of management of common headache disorders in primary care. *The Journal of Headache and Pain*, *8 Suppl 1*, S3–47. http://doi.org/10.1007/s10194-007-0366-y

Trescot, A. M., Datta, S., Lee, M., & Hansen, H. (2008). Opioid pharmacology. *Pain Physician*, *11*(2 Suppl), S133–153.

Tronvik, E., Stovner, L. J., Helde, G., Sand, T., & Bovim, G. (2003). Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA*, *289*(1), 65–69.

Tso, A. R., & Goadsby, P. J. (2014). New targets for migraine therapy. *Current Treatment Options in Neurology*, *16*(11), 318. http://doi.org/10.1007/s11940-014-0318-1

Literature Cited *(Continued 8)*

Yang, C.-P., Chang, M.-H., Liu, P.-E., Li, T.-C., Hsieh, C.-L., Hwang, K.-L., & Chang, H.-H. (2011). Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. *Cephalalgia: An International Journal of Headache*, *31*(15), 1510–1521. http://doi.org/10.1177/0333102411420585

(n.d.). Retrieved June 18, 2015, from http://www.gastrosource.com/11674565?itemId=11674565