European Headache School
Belgrade
2012

MIGRAINE
PROPHYLACTIC DRUG TREATMENT

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WHY MIGRAINE PREVENTION?

- 60% of migraineurs have 1 or more severe attacks per month
  - 25% experience 4 or more severe attacks per month

American Migraine Study II, Lipton et al, 2001

- Not all patients respond adequately or can tolerate abortive treatments
- Use of abortive treatments should be limited to 2 times per week
  - Avoid medication overuse

Why Migraine Prevention?

- Abortive agents may not adequately control frequent or disabling auras
- Prolonged or frequent episodes of pain may lead to changes in pain generators and more frequent migraines
- Only 5% of all migraineurs use preventive therapy to control their attacks

Lipton et al, 2002

- Nonpharmacological preventive strategies (biofeedback, relaxation training, cognitive behavioral therapy) are also underused

Goals Of Prophylactic Treatment

- Decrease attack
  - ✓ frequency
  - ✓ intensity
  - ✓ duration
- Improve responsiveness to acute therapy
- Improve function and decrease disability
- Prevent disease progression

The US Headache Consortium Evidence-Based Guidelines. May 2000

When To Use Preventive Medications?

- Indications are not evidence based but are the results of expert consensus and vary from guidelines to guidelines

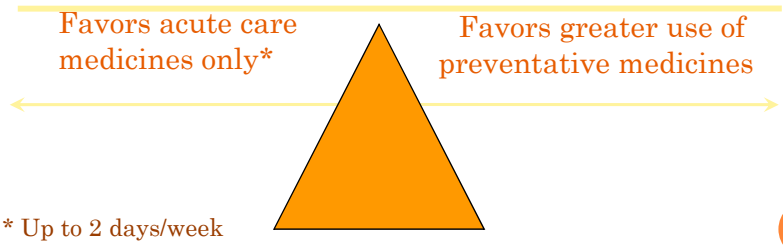
- Migraine significantly interferes with patient's daily routine and impairs quality of life despite acute medications
- Frequency of attacks ≥2 per month
- Acute medications contraindicated, ineffective, intolerable AEs, or overused
- Frequent, very long or uncomfortable auras
- Uncommon migraine conditions (attacks with a risk of permanent injury)
- Patient preference

EFNS Task Force 2009, US Evidence Based Guidelines 2004

Prophylactic Migraine Therapy

- Not disabling
- Short duration
- Good response to acute care medications

- Disabling
- Long duration headaches
- Poor response to acute care medicines



* Up to 2 days/week

Rapoport AM, Adelman JU. *Am J Managed Care*. 1998:531-544.

Principles of Successful Migraine Prevention

- "Start low, go slow"

  - Increase the dose until therapeutic effects develop, ceiling dose is reached or side effects become intolerable
  - May control headaches at lower dose than other indications for given preventative
  - Migraineurs can be particularly sensitive to drug side effects
  - Do not go so slow that no response is seen and patient gets discouraged

Principles of Successful Migraine Prevention

- Use lowest effective dose
  - But maximize dose before assuming agent is ineffective
- Allow adequate time to evaluate efficacy
  - May not see response for 8 to 12 weeks
  - This means that the drugs should be stopped within the first 3 months only due to side effects and not due to inefficacy
- Consider comorbid issues
  - Affective disorders, anxiety, epilepsy, ischemic cerebral, and other vascular diseases

Principles of Successful Migraine Prevention

- Ensure no contraindication to migraine treatment secondary to comorbidity and that comorbid treatment does not interfere with migraine treatment
- Limit frequent analgesic use, which can interfere with prophylaxis
- Provide appropriate acute medications for breakthrough migraines
- Use headache diaries

Principles of Successful Migraine Prevention

- Aim for monotherapy
  - If failure with multiple attempts at monotherapy with several classes, use a co-pharmacy approach combining classes of preventatives to treat migraine at several points in its pathophysiology
- The duration of an effective migraine prophylaxis should be at least 6 months
- Re-evaluate therapy
  - Drug holiday should be tried time to time
- Set appropriate patient expectations

Migraine Preventive Agents

- On average, each of preventive drugs has a therapeutic gain of approximately 25% with 50% of patients experiencing 50% efficacy, and all of the drugs have significant side effects
- There are no comparative studies showing a general superiority of one drug over another in migraine prophylaxis
- The choice of an appropriate drug is therefore based more on the potential side effects and comorbidities of a patient rather than on efficacy

EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, 2009

Drug Classes

Prophylactic drugs with good efficacy and tolerability
Betablockers
Antiepileptic drugs
Calcium channel blockers
NSAID
Antidepressants
Miscellaneous drugs

Mechanisms Of Action

- All effective drugs for migraine prophylaxis have been detected empirically
  - No drug has been developed based on the pathophysiological mechanisms of migraine
- Central and peripheral mechanisms of action
  - Raising the threshold to migraine activation by stabilizing more reactive nervous system
  - Enhancing antinociception
  - Inhibiting cortical spreading depression (CSD)
  - Inhibiting peripheral and central sensitization
  - Blocking neurogenic inflammation
  - Modulating sympathetic, parasympathetic or serotonergic tone

Silberstein et al., 2004

Mechanisms Of Action

- Valproate, topiramate, amitriptyline and propranolol inhibit CSD in rats, normalize neuronal firing and increase a genetically lowered and environmentally modified threshold for neuronal discharge by blocking excitatory glutamate-mediated or inhibiting gamma-aminobutyric acid (GABA)-mediated central activities
- Amitriptyline, candesartan and magnesium may act by restoring central nociceptive dysmodulation

Cassuci et al, 2008

Drugs Of First Choice For The Prophylactic Drug Treatment Of Migraine

Substances	Daily dose (mg)	Level
Beta blockers		
Matoprolol	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

EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, 2009

Drugs Of First Choice

- Beta blockers
  - 74 controlled trials consistently showed effectiveness of propranolol and metoprolol
  - Drugs of first choice in patients with hypertension, angina
  - Contraindications: asthma, insulin dependent diabetes
  - Adverse events: fatigue, depression, sleep disturbances, decreased exercise tolerance, orthostatic hypotension
  - Fairly well tolerated

Linde K et al, Cochrane Database Syst Rev 2004

Drugs Of First Choice

- Flunarizine
  - Non-specific calcium channel blocker
  - Female patients seems to benefit from lower doses (5 mg) than mail patients (10 mg)
  - In children and adolescents: 5 mg/day or every other day
  - Adverse events: depression, parkinsonism, weight gain

Diener HC, 2000

Drugs Of First Choice

- Topiramate
  - Has consistently shown efficacy in four large and well-powered trials
  - Adverse effects: paresthesias (reduced by taking 20-40 mEq of KCL per day), cognitive impairment, renal stone formation, acute myopia and secondary angle-closure glaucoma
  - Desirable side effect-weight loss 4-5% of body weight
  - The side effects leading to a cessation of intake occur nearly exclusively during the titration period
  - Topiramate is also efficacious in the prophylaxis of chronic migraine and in migraine with medication overuse

Brandes et al, 2004, Diener HC et al, Cephalalgia 2007
Silberstein SD et al, Headache 2007

Drugs Of First Choice

- Valproic acid
  - Has shown a reduction in migraine attack frequency in several placebo-controlled trials
  - Efficacy equal to propranolol
  - Adverse effects: nausea, vomiting (decreases over time), tremor, hair loss, weight gain, multiple ovarian cyst formation, teratogenic effects-neural tube abnormalities
  - Contraindication: pregnancy, history of pancreatitis, hepatic disorders

Chronicle E, Anticonvulsant drugs for migraine prophylaxis. Cochrane Database Syst Rev 2004

Drugs Of Second Choice

Substances	Daily dose (mg)	Level
Amitriptyline	50-150	B
Venlafaxine	75-150	B
Naproxen	2x250-500	B
Petasites	2x75	B
Bisoprolol	5-10	B

*Less efficacy in clinical trials than the drugs of first choice or tested in a small number of less well-designed trials, or more side effects

EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, 2009

Drugs Of Second Choice

- Amitriptyline
  - Useful in treating chronic pain conditions, including headache, independently of the presence of depression
  - Amitriptyline has only shown efficacy in 16 smaller and older trials
  - Dose range is wide and must be individualized
  - Adverse effects: dry mouth, dizziness, mental confusion, constipation, blurred vision, urinary retention, weight gain.
  - First line drug – when migraine co-exists with
    - Tension type headache
    - Another chronic pain condition
    - Disturbed sleep
    - Depression

BASH guidelines, 2004

Drugs Of Second Choice

- Venlafaxine
  - Selective serotonin and norepinephrine reuptake inhibitor
  - Efficacy is shown in one placebo controlled and two open trials, on average better tolerated than amitriptylin
- Naproxen
  - In controlled clinical trials, naproxen sodium demonstrated better efficacy than placebo and efficacy similar to propranolol
  - Adverse events: gastrointestinal and renal
  - Short term prophylaxis in menstrual migraine

Ozyalcin 2005, Solomon 1989

- Herbal remedies
  - Petasites (butterbur) is effective in migraine prevention (Level A)

AAN and AHS Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults, 2012

DRUGS OF THIRD CHOICE

Substances	Daily dose (mg)	Level
Acetylsalicylic acid	300	C
Gabapentin	1200-1600	C
Magnesium	24 mmol	C
Tanacetum parthenium	3x6.25	C
Riboflavin	400	C
Coenzyme Q10	300	C
Candesartan	16	C
Lisinopril	20	C
Methysergide	4-12	C

*only probable efficacy

EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, 2009

DRUGS OF THIRD CHOICE

- A very high doses of riboflavin (vitamin B_2) of 400 mg per day, and magnesium 24 mmol were also efficacious in some smaller placebo-controlled trials as well as coenzyme Q10 (300 mg/day)

- Methysergide
  - The 5-HT antagonist, one of the most effective antimigraine agent
  - Can be recommended for short term use only (maximum 6 months per treatment period)
  - Side effects: huge weight gain, tiredness, retroperitoneal pericardial and subendocardial fibrosis, major vessel constriction
  - Should not be combined with triptans
  - Very refractory, severe migraine patients

Pittler MH, 2004, Silberstein 1998

The Role Of Comorbidity

- Therapeutic opportunities
  - Treat two disorders with a single drug
    - Hypertension or angina—use ß-blocker
    - Depression—use TCAs or SNRIs
    - Epilepsy or mania—use valproic acid or topiramate
- Therapeutic limitations
  - Avoid ß-blockers with depression, asthma, or hypotension
  - Avoid TCAs, valproic acid in obese patients
  - Avoid TCAs, ß-blockers and Ca channel blockers in elderly with cardiac disease

Evans, Mathew, 2006

Preventive Treatment: Drug Choice

			Comorbid condition	
Drug	Efficacy	Side effects	Relative contraindication	Relative indication
Antiepileptics				
Valproic acid	4+	2+	Liver disease, pregnancy, hematologic disorders	Epilepsy, mania, impulse control
Topiramate	4+	2+	Renal disease	Epilepsy, mania
Betablockers			Asthma, depression, CHF, Raynaud's disease, diabetes	Hypertension, angina
Antidepressants				
TCAs	4+	2+	Mania, urinary retention, heart block	Neuropathic pain, depression, insomnia
SSRI, SNRI	2+	1+	Mania	Depression, OCD

Adapted from Gray RN et al. *Drug Treatments for the Prevention of Migraine. 1999*

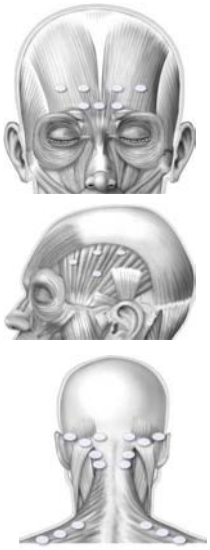
Preventive Treatment: Drug Choice

			Comorbid condition	
Drug	Efficacy	Side effects	Relative contraindication	Relative indication
NSAIDs				
Naproxen	2+	2+	Ulcer disease, gastritis	Arthritis
5-TH_2Antagonists				
Methysergide	4+	4+	Angina, PVD	Orthostatic hypotension
Other				
Riboflavin	2+	1+		
Feverfew	2+	2+		Preference for natural products
Botulinum toxin	2+	1+	Myasthenia gravis	Dystonia, spasticity
Petasites	2+	1+		
Candasartan	2+	1+		Hypertension

Botulinum Toxin A

- Proposed mechanism of action: Onaboulinumtoxin A inhibits the sensitization of peripheral trigeminal sensory fibers, which modulate the activity of central trigeminal neurons, and thus, indirectly leads to the inhibition of migraine headache
- Local injections of botulinum toxin have shown no superiority over placebo in nearly all controlled trials in episodic migraine and TTH

Botulinum Toxin A



- The PREEMPT clinical program confirmed onabotulinumtoxin A as an effective, safe, and well-tolerated headache prophylaxis treatment of adults with **Chronic Migraine**
- Significantly reduces headache frequency, headache-related disability, improves functioning, vitality, and overall health-related quality of life

Aurora SK et al, Diener HC at al. Cephalalgia 2010

Drugs Which Cannot Be Recommended In Migraine Prophylaxis

Substances
Selective serotonin reuptake inhibitors
Lamotrigine
Oxcarbazepine
Acetazolamide
Clomipramine
Clonidine cyclandelate
Lanepitant
Montelukast
Homeopathic remedies

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Menstrual Migraine

- Short term drug prophylaxis with 2 × 500 mg of naproxen per day over 5 days before and during the menstrual bleeding can be tried: however, the evidence is weak

  Sances et al, 1990, Szekely et al, 1989

- Transdermal estradiol, not <100 µg for 6 day perimenstrually as a gel or a patch

  De Lignieres 1986

- In some women menstrual migraine attack is only postponed to the days after the menstrual bleeding

Menstrual Migraine

- Triptans such as 2 × 1 mg naratriptan, 2 × 25 mg sumatriptan or 1 – 2 × 2.5 mg frovatriptan over 5 – 6 days have been efficacious in preventing menstrual migraine attacks in double-blind placebo-controlled trials

  Silberstein et al 2004, Brandes 2009, Mannix at al 2007

- Frovatriptan is established as effective and should be offered for short-term menstrual migraine prevention

  Level A recommendation

- Naratriptan, zolmitriptan are probably effective and should be considered for short term menstrual migraine prevention

  Level B recommendation

AAN and AHS Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults, Neurology 2012

Migraine Prophylaxis In Pregnancy

- Controlled trials on migraine prophylaxis in pregnancy are not available
- Only magnesium and metoprolol are recommended during pregnancy

Level B recommendation

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- Non-drug treatment procedures such as relaxation therapy, biofeedback and acupuncture can be tried

Evers, 2008

Migraine In Children And Adolescents

- The efficacy of flunarizine (5-10 mg/day) in children has been proven in three placebo-controlled trials
- Topiramate has also shown efficacy in a daily dose of between 15 and 200 mg in children and adolescents
- Propranolol 40- 80 mg/day might be efficacious

Lewis D, 2004, Winner P 2006

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Reasons Of Failure Of Preventive Therapy

- Incorrect diagnosis
- Inadequate doses
- Inadequate treatment period
- Failure to recognize comorbidities
- Acute medications overuse
- Unrealistic expectations

Evans, Mathew, 2006

Summary Of Prevention

- It is estimated that only about 10% of all patients who require preventive treatment receive adequate drug prophylaxis
- Fear of side effects, tolerance, addiction
- The efficacy of most drugs is limited
- Freedom of migraine is rarely achieved
- The combination of different migraine prophylactic drugs should be evaluated in further clinical research
- Patients and physicians education may be the key to successful prophylaxis

BELGRADE, MAY, 2012

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