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 $\geq 2$ 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

Favors acute care medicines only*  Favors greater use of preventative medicines

* Up to 2 days/week

**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

- 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

<table>
<thead>
<tr>
<th>Prophylactic drugs with good efficacy and tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betablockers</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>NSAID</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Miscellaneous drugs</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose (mg)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matoprolol</td>
<td>50-200</td>
<td>A</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40-240</td>
<td>A</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>5-10</td>
<td>A</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>500-1800</td>
<td>A</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25-100</td>
<td>A</td>
</tr>
</tbody>
</table>

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 seem to benefit from lower doses (5 mg) than male 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

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*

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DRUGS OF SECOND CHOICE

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose (mg)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>50-150</td>
<td>B</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-150</td>
<td>B</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2x250-500</td>
<td>B</td>
</tr>
<tr>
<td>Petasites</td>
<td>2x75</td>
<td>B</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5-10</td>
<td>B</td>
</tr>
</tbody>
</table>

*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 amitriptyline

○ 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

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose (mg)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>300</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200-1600</td>
<td>C</td>
</tr>
<tr>
<td>Magnesium</td>
<td>24 mmol</td>
<td>C</td>
</tr>
<tr>
<td>Tanacetum parthenium</td>
<td>3x6.25</td>
<td>C</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>400</td>
<td>C</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>300</td>
<td>C</td>
</tr>
<tr>
<td>Candesartan</td>
<td>16</td>
<td>C</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20</td>
<td>C</td>
</tr>
<tr>
<td>Methysergide</td>
<td>4-12</td>
<td>C</td>
</tr>
</tbody>
</table>

*only probable efficacy

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

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### Drugs of Third Choice

- A very high doses of **riboflavin** (vitamin B₂) 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 β-blocker
    ○ Depression—use TCAs or SNRIs
    ○ Epilepsy or mania—use valproic acid or topiramate

○ Therapeutic limitations
  - Avoid β-blockers with depression, asthma, or hypotension
  - Avoid TCAs, valproic acid in obese patients
  - Avoid TCAs, β-blockers and Ca channel blockers in elderly with cardiac disease

Evans, Mathew, 2006

PREVENTIVE TREATMENT: DRUG CHOICE

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

Adapted from Gray RN et al. Drug Treatments for the Prevention of Migraine. 1999
# Preventive Treatment: Drug Choice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Side effects</th>
<th>Relative contraindication</th>
<th>Relative indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>2+</td>
<td>2+</td>
<td>Ulcer disease, gastritis</td>
<td>Arthritis</td>
</tr>
<tr>
<td>5-HT₂ Antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>4+</td>
<td>4+</td>
<td>Angina, PVD</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td>2+</td>
<td>2+</td>
<td>Preference for natural products</td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>2+</td>
<td>1+</td>
<td>Myasthenia gravis</td>
<td>Dystonia, spasticity</td>
</tr>
<tr>
<td>Petasites</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candasartan</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

## Botulinum Toxin A

- Proposed mechanism of action:
  - Onabotulinumtoxin 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_

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**Drugs Which Cannot Be Recommended In Migraine Prophylaxis**

<table>
<thead>
<tr>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>Clonidine cyclandelate</td>
</tr>
<tr>
<td>Lanepitant</td>
</tr>
<tr>
<td>Montelukast</td>
</tr>
<tr>
<td>Homeopathic remedies</td>
</tr>
</tbody>
</table>

_EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, 2009_
**MENSTRUAL MIGRAINE**

- Short term drug prophylaxis with $2 \times 500$ 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 $<100 \mu$g for 6 days 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

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**MENSTRUAL MIGRAINE**

- Triptans such as $2 \times 1$ mg naratriptan, $2 \times 25$ mg sumatriptan or $1 – 2 \times 2.5$ 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 et 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*

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

- 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*

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