Migraine

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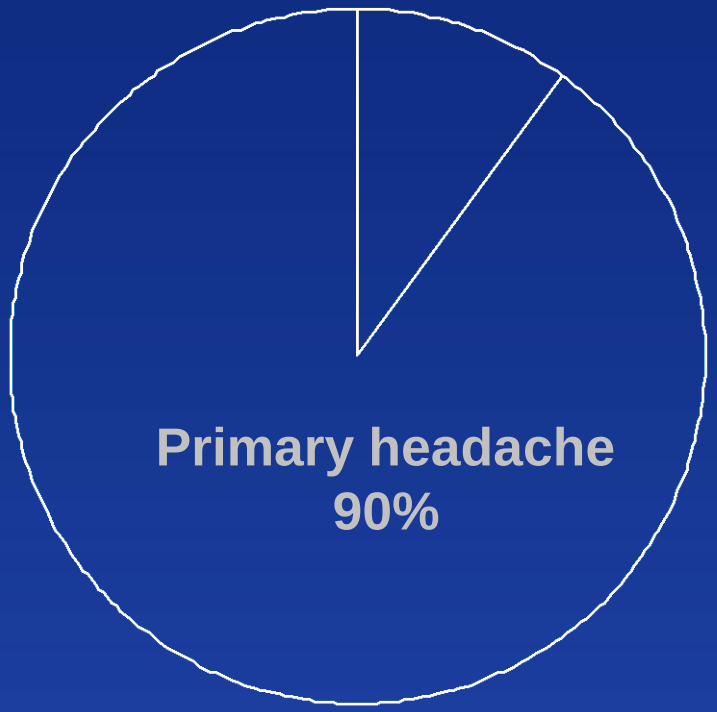
Clinical Pearls in Headache

- Rose Giammarco

Objectives

- 1. Migraine Diagnosis
- 2. Acute and Prophylactic Treatment
- 3. Medication overuse Headache

Classification of Headache



Primary headaches (No underlying cause)

- Migraine
- Tension-type
- Cluster headache
- Other misc headaches

Secondary headaches (Underlying cause)

- Medication overuse
- Head/neck injury
- Tumor
- Subarachnoid hemorrhage
- Meningitis
- … and many others

Adapted from the Headache Classification Committee of the IHS. *Cephalalgia* 1988; 8 (Supp 7):1-96.

Diagnosis of ‘common vs classic migraine’

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Migraine Without Aura

- 5 recurrent headaches
- Lasts 4 to 72 hours
- With 2/4
  - Unilateral
  - Pulsating (throbbing) quality
  - Worsening of the headache with movement
  - Moderate to severe
- Accompanied of 1/2
  - Nausea or vomiting,
  - Aversion to light, sound and/or osmophobia
- Not attributed to another disorder

Migraine With Aura

- All the criteria of migraine without aura +
  - Fully reversible homonymous visual symptoms: flickering lights, spots or lines and/or loss of vision
  - Fully reversible unilateral sensory symptoms: pins and needles and/or numbness
  - Fully reversible dysphasic speech disturbance
  - Symptom develops gradually over ≥5 minutes and/or in succession over ≥5 minutes
  - Each symptom lasts ≥5 and ≤60 minutes

Question #1:

What the Overall Approach to the Patient with Headache?

Approach to Treatment

- Non pharmacologic
- Acute treatment
- Prophylaxis

What is the first step?

- **Address lifestyle factors**

  stress, skipping meals, obesity, sleep hygiene, work schedules

  Avoid migraine triggers

  caffeine withdrawal, alcohol, sunlight, menstruation, barometric pressure changes

Explore Possible Lifestyle Changes and Non-Pharmacological Interventions

- Limited scientifically-validated data
- Some trigger factors have been validated
  - Irregular sleep-wake cycle (sleep deprivation/sleeping in/shift work)
  - Delayed or skipped meals
  - Stressful life events and poor coping with stress
  - Menstruation
  - Lack of exercise
  - Idiosyncratic exposures: certain foods, caffeine consumption/withdrawal, certain lights, computer screens, etc.
- The modifiable should be modified

Migraine: Planning Treatment Strategy

Define specific aspects of patient's migraine

(via headache and medication diary)

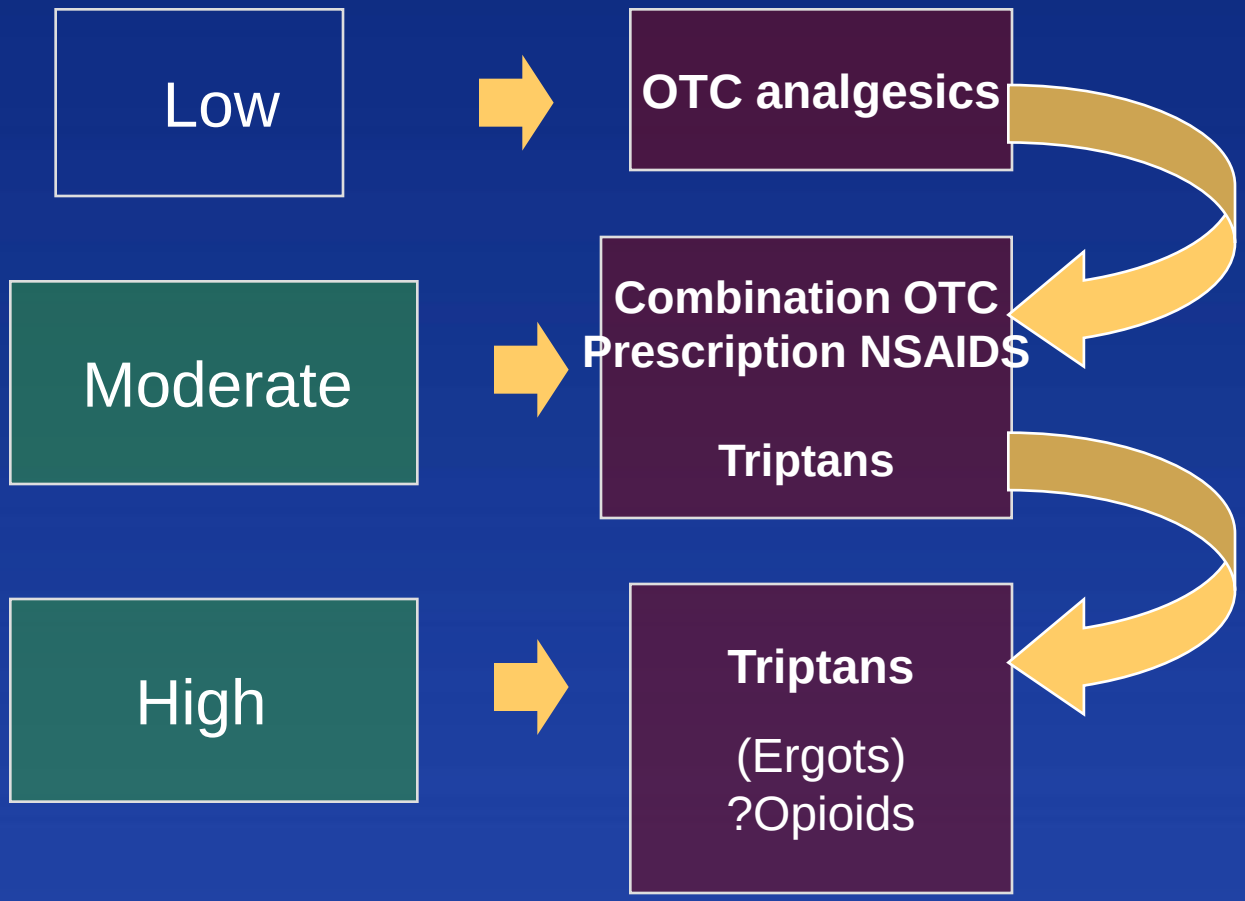
- Headache frequency
- Headache severity and degree of disability
- Attack characteristics (time to peak pain)
- Associated symptoms (nausea early or late)

- Patterns of migraine (i.e. menstrual, weekend)
- Trigger factors

- Previous treatment trials, response and side-effects
- Contraindications and comorbities

Stratified Care:

<u>Define the needs:</u>
MIDAS, clinical judgment



Stepped care within attacks :

according to immediate effect

Acute Migraine Treatment Principles

1. Treat according to degree of disability (stratified care)
2. Treat **<u>early</u>** in the migraine attack (*unless* attacks are too frequent)
3. If necessary, try several different triptans
4. Consider combination therapy (i.e. triptan & NSAID)
5. Treat a/t characteristics of the migraine:
   - Early or late peak headache intensity
   - Early of late nausea
   - Long duration attacks and headache recurrence

Acute Migraine Medications

- **Non specific**
  - **OTC analgesics**
  - **Prescription NSAIDs**
  - **Combination analgesics**
  - **Neuroleptics/anti-emetics**
  - **Corticosteroids**
  - **Opioids?!**

- **Specific therapy**
  - **Ergotamine/DHE**
  - **Triptans**

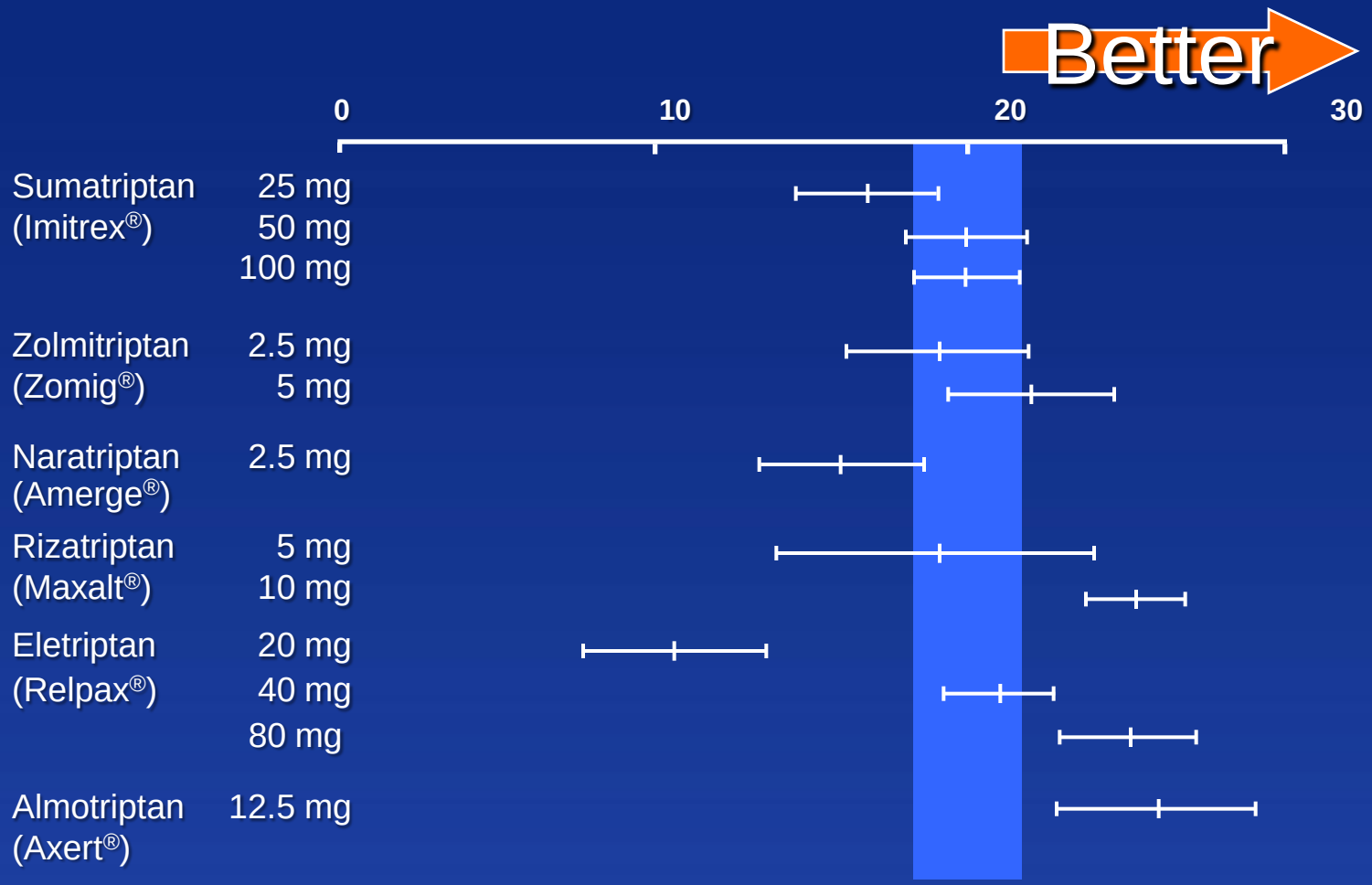
- Helpful in some patients
  - Mild or moderate intensity
  - Used in combination with specific therapy
  - Special populations
    (i.e. pregnancy, pediatrics, cardiovascular hx/risk factors)

- As much as possible try to avoid medications containing barbiturates, opioids

TRIPTANS: TREATMENT CHOICES

- Sumatriptan (IMITREX)
  - Tablet (25, 50, 100 mg)
  - Injection (6 mg)
  - Nasal spray (5, 20 mg*)
- Zolmitriptan (ZOMIG)
  - Tablet & melt (2.5, 5 mg)
  - Nasal spray (5 mg)
- Naratriptan (AMERGE)
  - Tablet (1, 2.5 mg)
- Rizatriptan (MAXALT)
  - Tablet & melt (5, 10 mg)
- Almotriptan (AXERT)
  - Tablet (6.25, 12.5 mg)
- Eletriptan (RELPAX)
  - Tablet (20, 40 mg)
- Frovatriptan (FROVA)
  - Tablet (2.5 mg)

Efficacy of Oral Triptans: Sustained Pain Free



Adapted from Ferrari MD et al. *Lancet* 2001;358:1668-75.

Clinical Considerations

Early Peak

- Almotriptan
- Eletriptan
- Rizatriptan
- Sumatriptan
- Zolmitriptan

Late Peak

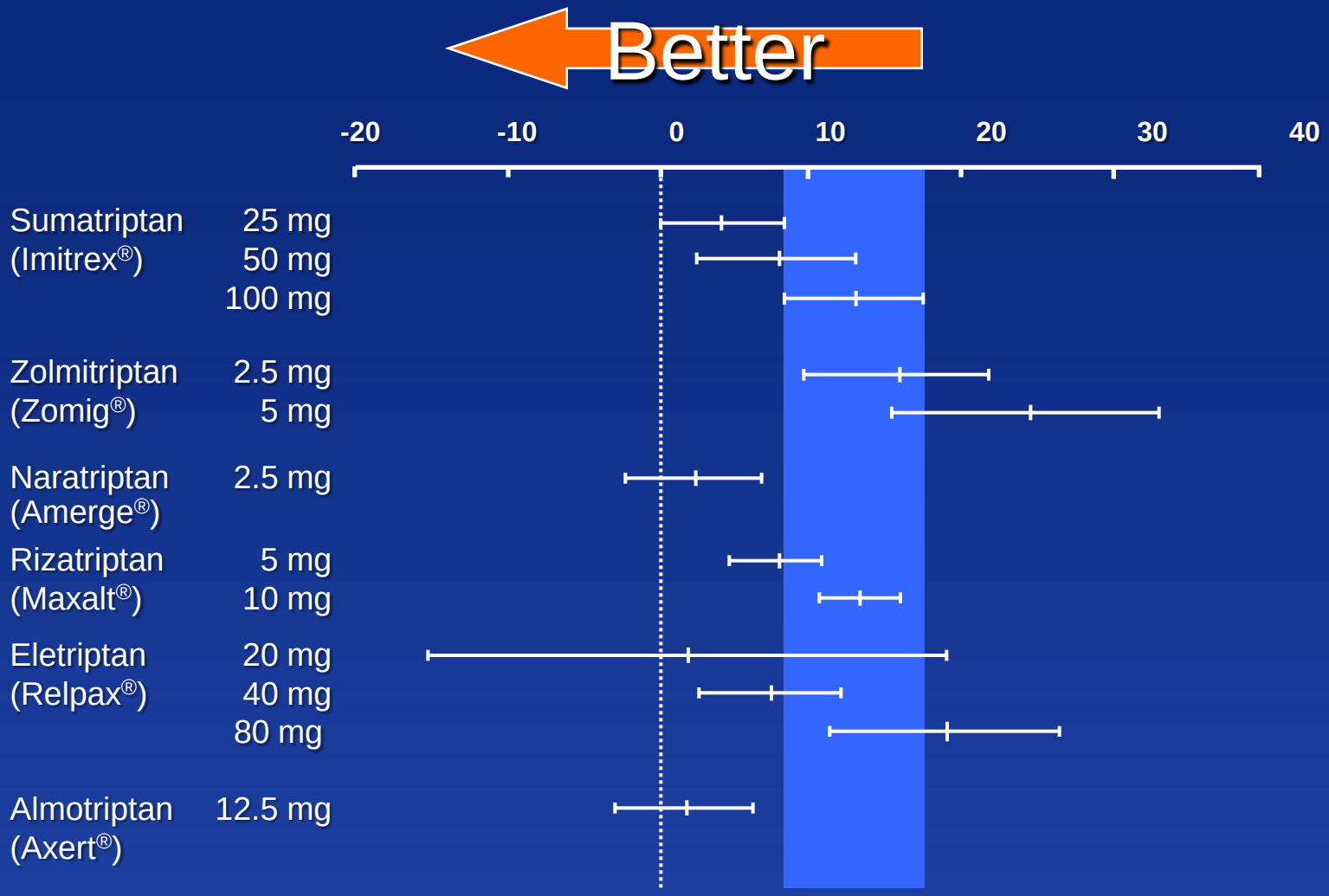
- Frovatriptan
- Naratriptan

Low AEs

- Almotriptan
- Naratriptan

Tolerability of Oral Triptans:

Placebo-subtracted Incidence of Any Adverse Events

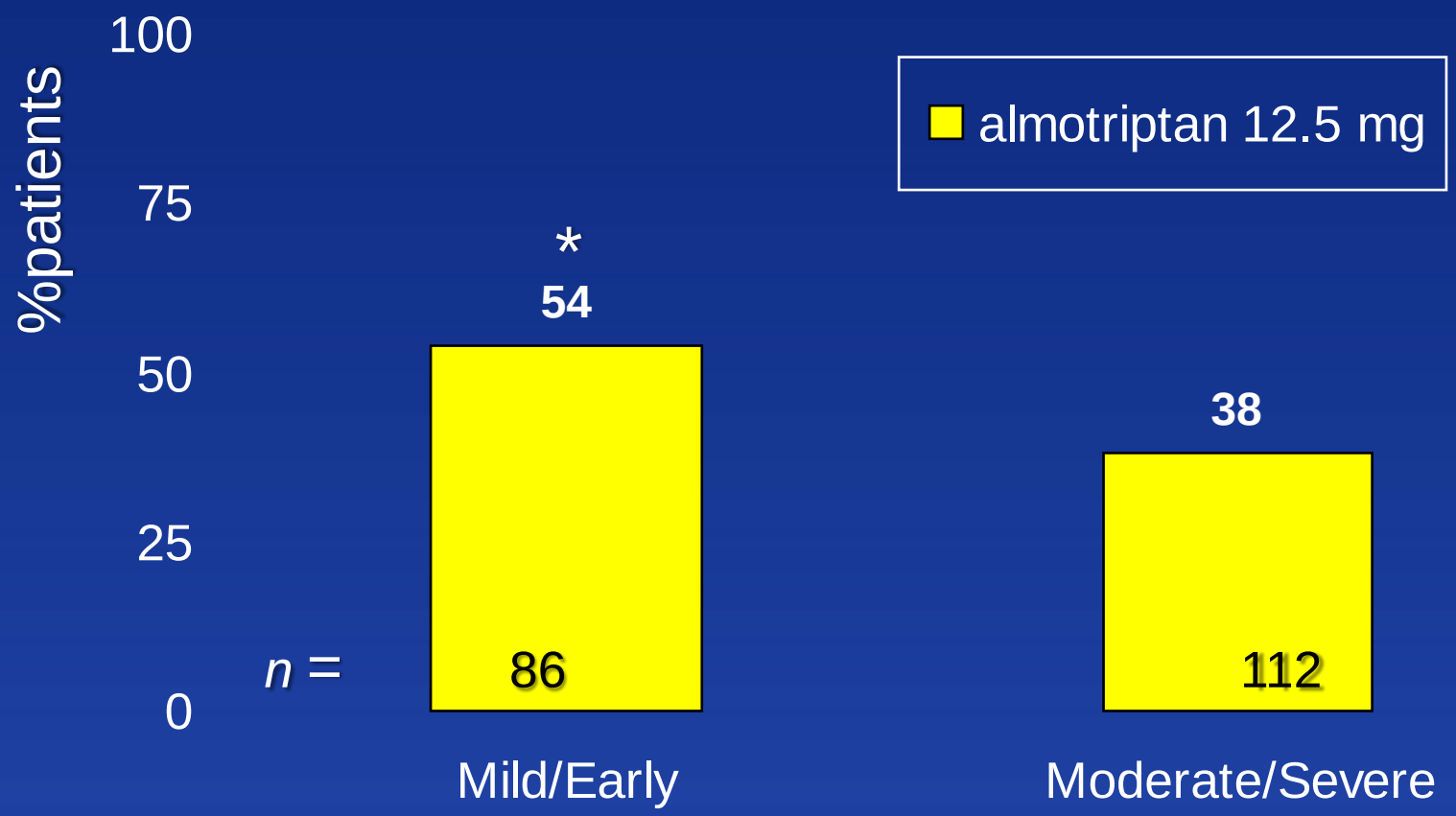


Adapted from Ferrari MD et al. *Lancet* 2001;358:1668-75.

AwM Study

Pain free at 2 hr- *AwM* population

- Almotriptan 12.5 mg was superior in the early/mild headache compared to moderate/severe headache



(**P* = 0.02)

Question #15:

Are Triptans Safe?

Triptan Safety
Consensus statement

- (1) Most of the data on triptans are derived from patients without known coronary artery disease.
- (2) Chest symptoms occurring during use of triptans are generally non-serious and are not explained by ischemia.
- (3) The incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low.
- (4) The cardiovascular risk-benefit profile of triptans favors their use in the absence of contraindications.

Headache 2004;44(5):414-425

Case

- Dx with migraine
- Rx diary, and a triptan
- Now returns in 6 mo with increasing headaches occurring 5 to 6 per month
- What do you do

Question #16:

What Do We Need to Know About Preventative Therapy?

Questions to consider

- What is your dx?
- Do you have any concerns?
- Would you consider prophylaxis and why?
- Which agent would you chose?

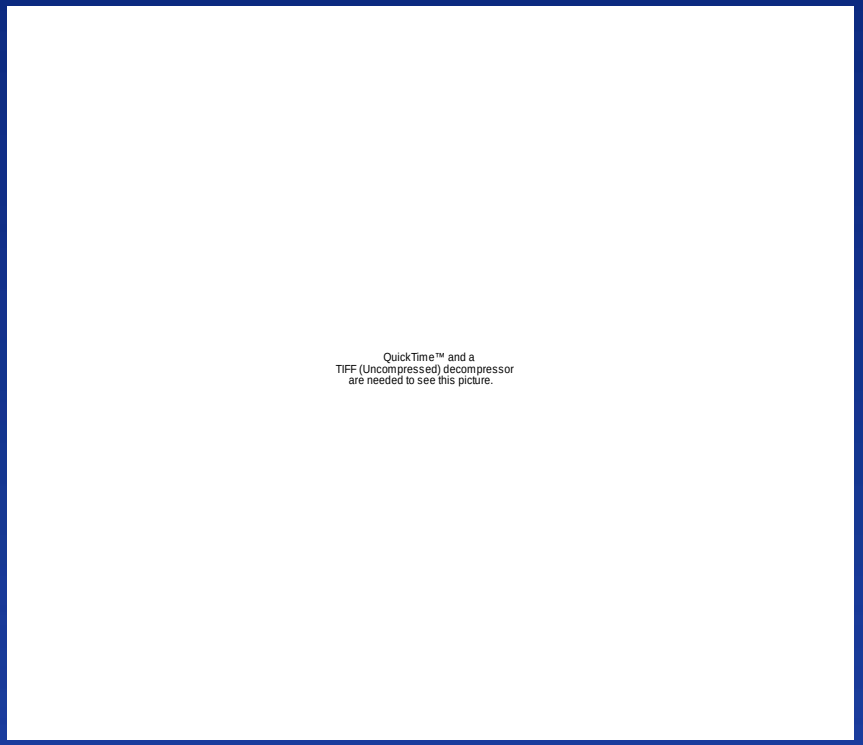
When should prophylactic therapy be considered?

Preventative medications

- Do I have t take it everyday?
- How long do I have to be on it?
- Side effects?
- What are the preventative medications?
- Keep a headache diary to moniter the effectiveness of your meds

When do you consider prophylactic meds?

- Substantial disability
- High headache frequency risks MOH
- Individualized treatment
- 25% of patients should be offered proph Rx



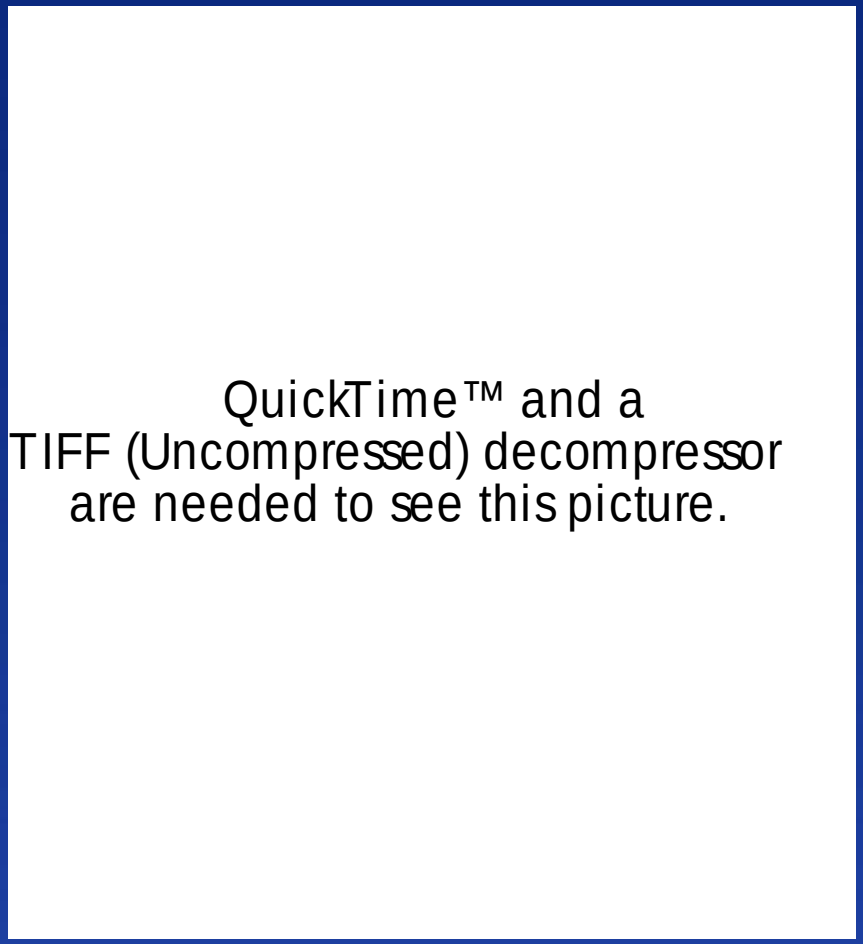
Preventive treatment

- **Goals?**
  - Reduce
    - h/a frequency
    - Duration
    - Severity
    - Medication requirements
    - Headache-related disability
  - ? Prevent migraine transformation into chronic migraine
- **What to expect?**
  - 50% obtain a reduction of ≥50% in the frequency of attacks in the second or third month of use
- **Monotherapy vs Polytherapy?**
  - Monortherapy preferred but polytherapy may be necessary
- **When ?**
  - When ≥ 3-4 severe attacks per month poorly controlled with symptomatic medication
  - When symptomatic medication needs to be used more than 2-3 days a week
  - Special situations preclude the use of effective acute medications
- **For how long ?**
  - 3 month minimum trial
  - If helpful, consider reduction and cessation after 12-18 months

Potential Outcomes to Rx

- Benefit with 50% reduction freq/intensity
- Improved response to symptomatic treatment
- Side effects necessitate discontinuation
- Insufficient response
- ‘Start low go slow’

Classes of Preventive meds



- Beta blockers
- Antidepressants
- Calcium channel blockers
- Neuromodulaters
- Serotonin antagonists
- Botox

Antiepileptics

- Divalproex sodium
- Topiramate
- gabapentin

Prophylactic Meds by quality of supporting evidence, clinical impression of efficacy and AE

Med Start dose	Quality of Evidence	Impression of Efficacy	AE Frequency	AE Incidence
Divalproex sodium 250 bid (500-1500 d)	A	Effective	Frequent at higher doses	Nausea15-46%, somnolence7-30% Tremor13-16%, dizzy20%
Topiramate 25 hs (50-200m/d)	A	Very effective	Frequent especially at higher doses	Paresthesias34-56%, wt loss5-11%, altered taste5-20%,anorexia8-17%, Fatigue9-24%,memory4-15
Gabapentin 300bid (900-3600d)	B	Effective	Occasional	Somnolence25% Dizziness26%, Asthenia22%

Antidepressants

Med Start Dose	Quality of Evidence	Impression of Efficacy	AE Frequency	AE Incidence
Amitriptyline 10m/hs (20-50 hs)	B	Very Effective	Occasional	Dry mouth35-69%, drowsiness20-35%
Venlafaxine 37.5 (75-150 od)	B	Effective	Occasional	Nausea23-45%, vomiting30%, Drowsiness12-14%

Antihypertensives

Med Start Dose	Quality of Evidence	Impression of Efficacy	AE Frequency	AE Incidence
Propranolol 20bid (40-160)	B	Effective	Infrequent	Fatigue(22%) decrease HR BP common
Nadolol 80/d (80-240d	B	Effective	Infrequent	Drowsy(13&)
Flunarizine 5/d (5-10d)	B	Effective	Occasional	Sedation 7-10%,wt gain 15-21%
Verapamil 40tid (40-80tid)	C	Somewhat effective	Infrequent	Mild constipation 43%
Lisinopril 20/d	B	Effective	Infrequent	
Candesartan 16/d	B	Effective	Infrequent	

Other

Med Start dose	Quality of evidence	Impression of efficacy	AE frequency	AE Incidence
Pizotifen .5tid (1.5-3d)	B	Effective	Occasional	Wt gain 21-41% Sedation 37-50%
Botulinum type A 100u	B	Ineffective	Infrequent	

How to chose ?

First Line Agents	Second line agents	Third line agents
Amitriptyline	Topiramate	Flunarizine
Propranolol	Gabapentin	Pizotifen
Nadolol	Venlafaxine	Divalproex NA
	Candesarten	
	Lisinopril	
	Magnesium	
	butterbur	
	CoQ10	
	Riboflavin	

Special Considerations	Agent
HP CV disease	Propranolol,nadolol,lisinopril, candesarten
Insomnia	Amitriptyline
Mood disorder	Amitriptyline,venflaxine
Seizure disorder	Topiramate,divalproex, gabapentin
Pregnant or attempting	magnesium
Obesity	topiramate
Poor tolerance A/E	Ribo,Coq10,butterbur,propranol lisinopril,candesarten

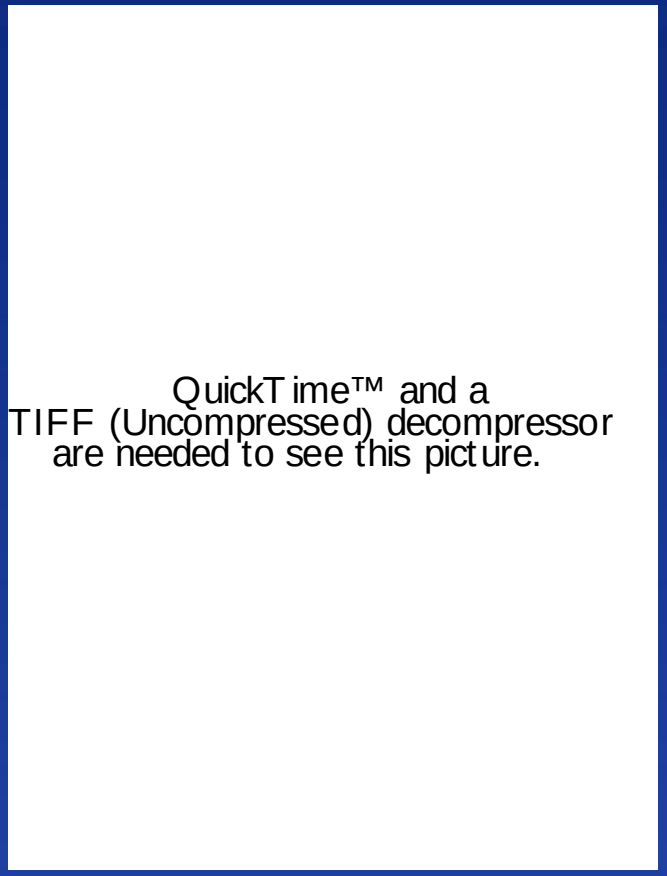
Vitamins, Minerals, Herbal

Med Start Dose	Quality of Evidence	Impression of Efficacy	AE Frequency	AE Incidence
Riboflavin 400/d	A	Somewhat effective	Infrequent	
Magnesium 300d (300-600d)	B	Somewhat effective	Occasional	Soft stool, diarrhea 20%
Feverfew 6.25d (6.25-18.75d)	B	Ineffective	Infrequent	
CoQ10 100tid	B	Effective	Infrequent	
Butterbur 50tid (100-150/d)	A	Effective	Infrequent	Burping 25%

What about Botox?

- PREEMPT trial
- Chronic migraine
- 155-200 units q 3mo
- Reduction in HA days and use of overused meds
- Well tolerated
- Cost

Start low and go slow



When do we discontinue meds?

- Studies suggest most patients relapse after stop meds up to 75%Woeber C.etal.Cephalalgia 1991;11;251-6
- Topiramate study found that within 1month patients on placebo vs top. deteriorated
- Therefore suggest pts be stopped at some point to see if still needed
- Continuation of proph meds in the difficult migraine patient with high disability may be recommended
- Follow up every 3-6 mo required to evaluate continued benefit

Clinical Pearls

- Choice of proph based on comorbidity, contraindications, efficacy and AE
- Proph considered when QOL affected despite symptomatic RX or at risk of MOH
- Period of proph not clear. Regular followup to ensure benefit

Patient MAL: Presentation, Nov15th, 2005

- 44 year old female with chronic daily headache.
- Long history of intermittent but infrequent headaches which would occasionally put her in bed.
- Current headaches are bifrontal, throbbing, worse on exertion, and with nausea and phonophobia.
- Current meds included amitriptyline, atenolol, and 6 Percocet / day, occasional Tylenol 3 and 1

Audience Discussion

DIAGNOSIS?

Differential of CDH

- ***Primary Headache***
- Chronic Migraine
- Chronic TTH
- Hemicrania Continua
- NDPH

- ***Secondary Headache***
- Chronic HA injury
- Medication overuse
- Cervicogenic HA
- other

8.2 Medication-overuse headache

- A.Headache present on ≥15d/mo fulfilling criteria C and D
- B.Regular overuse for >3 mo of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
- C.Headache has developed or markedly worsened during medication overuse
- D.Headache resolves or reverts to its previous pattern within 2 mo after discontinuation of overused medication*

*ICHD-2R eliminates this requirement
Ceph2004:24:Suppl 1

Ceph2005;25:460-465

8.2 Medication-overuse headache

- 8.2.1 *ergotamine*-overuse headache
- 8.2.2 *triptan*-overuse headache
- 8.2.3 *analgesic*-overuse headache
- 8.2.3 *opioid*-overuse headache
- 8.2.5 *combination analgesic*-overuse HA
- 8.2.5 Medication-overuse headache attributed to *combination of acute medications*
- 8.2.7 headache attributed to other medication overuse
- 8.2.8 Probable medication overuse

Clinical features of MOH

- Escalation in HA frequency
- Early morning awakening with headache
- Daily headache may resemble TTH
- May be precipitated by exertion
- Escalation of symptomatic meds
- Headache recurs after medication ‘wears off’
- Chronic daily headache with episodic more severe headache resembling ‘migraine’

What Contributes to MOH

- Too little, too much
- Subtherapeutic trial
- Need for combination Rx
- Wrong drug, wrong diagnosis
- Non compliance
- Unrealistic expectations
- Ineffective acute Rx
- MOH reducing effectiveness of prevention Rx

Lipton, neuro 2003, 60(7)1064-70

Management

- Goals;
- Stop the percocet, tylenol
- Reduce the headache frequency
- Be sure the patient is ‘on side’ with treatment
- Set start and stop date with realistic expectations
- ‘Not cure’ vs ‘Control”

To wean or not?

- Most wean can be done as OP
- Some requires infusion
- Consider comorbidity and agent used

Approaches to Treatment

- ***Slow wean***, addition of prevention,acute Rx within limits <2day/wk(agent other than the one overused)
- ***Abrupt withdrawal***, prevention, +/- ‘bridging’
- Set a short term ‘stop date’
- Consider short term steroid
- Multidisciplinary approach

Treatment Options

- Raskin Protocol
- Repetitive IV DHE tid up to 1 mg preceded by maxeran 10 mg 15 min prior
- Can use gravol 25 IV po or Cogentin 1mg for dystonic reaction
- Stop analgesics
- 3 days Neurology,1986;36

- Consider DHE 1mg bid or tid (self injection)
- Preceded by 10 mg Maxeran IM
- DHE nasal

IV Valproate for the acute Rx

- 300-500 mg over 5 min 100 ns
- Not in pregnancy
- Repeat if needed

Mathew NT, Headache 2000;40 (9)

Who needs admission?

- Treatment failure as outpatient
- Psychologic or medical ER (withdrawal, angina,seizures)
- Comorbid conditions make compliance difficult
- Poor support system
- Poorly motivated patient

BRIDGING MEDICATION?

Options for Weaning

- 1.*Out patient, slow wean*, +prevention and migraine specific meds with limitations
- 2.*Abrupt discontinuation of meds*, ‘bridging’ and addition of prevention
- 3.*Infusion as the bridge* with addition of prevention
- 4.*Multidisciplinary*: Wean, infusions as bridge, prevention, use of nutritionist, nurse educator, psychologist, social work, massage therapist etc

Or…….
Abrupt 'Stop' with 'Bridging"

- 1. Stop overused drug
- 2.Initiate 'bridge for 7-10 days

Consider

NSAIDS Naproxen 500 bid

Steroids Dexamethasone 4mg bid 4 days

Prednisone 60mg/day taper by 20 every 2days

Or

Dexamethasone 4mg bid 4 days, OD 4days

Krymchantowski. Ceph 2003;23. 982-93

Role of Triptans

- Suma 25mg tid 10 days or until headache free
  Drucker,HA.1998;38;687-690
- Nara 2.5 bid 1 week Krymchantowski.Ceph 2003,23;982-993
- *Ergots*
- DHE nasal bid or tid 7-10 days

  Saper HA 2006 46;(4)212-220

OP Abrupt 'Stop'

- Begin prevention
- Amitriptyline, Nortriptylline 25 hs-50hs
- Beta blockers,metoprolol 25 day 1, 50mg day2/nadolol
- Botox
- When bridging complete, provide migraine specific med with limits (2 days/wk)
- Consider steroid if not used and patient is having trouble!

Prednisolone does not reduce withdrawal headache: a RDBP study **Boe MG,Neuro 2007**

- 26 males,74 females
- RDBPCT
- Hospitalized 3 d for med withdrawal
- Pred 60, 40,20 over 6 days vs placebo
- Conclusion:
- Prednisone had no effect on withdrawal HA

Prednisone in withdrawal therapy Pageler et al Cephpalalgia,2007,28

- 20 pts RPCDB underwent in pt withdrawal
- Placebo or prednisone 100 first 5 days
- Total number of hours with severe HA within first 72 hours lower in prednisone vs placebo group(18.1 vs 36.7)
- ? prednisone use in withdrawal to decrease headache and withdrawal symptoms

Treatment of Medication overuse Headache-guideline of the EFNS headache panel

Evers S.et al. EurJNeuo 2011.18:1115-1121

- Pts with MOH should be offered advice and teaching to encourage withdrawal (B)

- There is no general evidence whether abrupt or tapering withdrawal Rx should be preferred.for overuse of analgesics, ergots, triptans, abrupt is recommended.Opioids, benzos,barbs, tapering should be offered. (GPP)

- The type of the withdrawal Treatment does not influence the success and the relapse rate.(A)

- In pts with opioid,benzo and barb overuse, with severe psych comorbidity or with failure of a previous OP withdrawal Rx, IP Rx should be offered (GPP)
- Individualized preventive meds should be started first day of withdrawal or even before if applicable C
- Topamax 100(200) is probably effective in Rx of MOH(B)
- Steroids(60 prednisone) and amitriptyline (up to 50) are possibly effective in Rx of withdrawal(GPP)
- Pts after withdrawal should be followed regularly to prevent relapse (GPP)

Detox for MOH is not necessary

Diener HC.Ceph apr 2012

- 1.Pts should be encouraged and counseled about MOH motivate them withdraw meds
- 2.all should be offered non drug Rx and additional preventive meds.(evidence for topiramate and Botox)
- 3.No evidence for other drugs (elavil, aba valproate small trials)
- 4.Remaining should be offered inpt detox with behavioural, cognitive and exercise then prevention

Longitudinal Population Based Study **Bigal et al Headache 2008;48;**

- Episodic migraineurs average annual incidence of TM 2.5%
- Freq of HA and use of specific classes of meds are associated with development of TM
- Opiates and barbs associated with increase risk of TM
- High freq HA at baseline increase the risk (>3/mo)
- Increased monthly NSAIDS protected if <10-14 d/mo

Studies have shown relapse rate of overuse after successful withdrawal is nearly 40%. [1.2.]

1.Diener et al Lancet Neuro, 2004;3

2.Zidverc-Trajkovic Cephalalgia.2007

Cornerstones of Treatment on Medication Overuse

- Patient education.
- Stop medication overuse.
- Plan for treatment of severe acute attacks.
- Prophylaxis.
- Support and follow up.

Clinical Pearls

- Make the diagnosis
- Non pharm approach first!
- Assess disability
- Consider comorbidity in choosing prophylaxis
- Start low and go slow
- MOH prevent it!
- Consider ‘bridging’