MIGRAINE CAVEATS

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1. Nearly all-periodic debilitating headaches are migraine.

2. Use triptans ASAP. Patients, who treat when pain is mild, before progression to moderate/severe intensity, achieve high pain-free efficacy.

3. When the pain is not treated early, it may become more refractory due to the development of central sensitivisation.

4. Look for migraine co-morbidity: depression, anxiety, fibromyalgia, bipolar disorder, IBS, endometriosis

5. Episodic tension-type headaches (ETTH):

   TTH in persons with migraine has "migraine-like" mechanisms; TTH in persons without migraine is biologically distinct:
   - In persons with migraine, TTH response to triptans.
   - In persons without migraine, TTN does not respond to triptans.

6. There are 5 phases of migraine:
   a. Prodrome
   b. Aura
   c. Early Headache
   d. Late headache
   e. Postdrome

7. Early morning migraine:
   48% occur between 4 a.m. and 9 a.m., often severe at onset, and best responding to SC Imitrex.

8. Match T-max (hrs) to peak migraine intensity (hours) for best initial tritan choice.
   Fastest: 20 min → Slowest: 3 hours
   IC Imitrex SC → Imitrex IN → Maxalt PO
   → (Imitrex, Zomig PO + IN, Axert PO, Relpax PO)
   → Amerge PO → Frova PO

9. The more lipophilic a triptan is, the more CNS drug penetration, the higher the CNS adverse events:
   Least → most
   Imitrex → Amerge → Zomig → Maxalt → Relpax

10. All triptans are SHT 1B/1D agonists and have the potential to constrict human coronary arteries.

    Chest symptoms are rarely reflective of cardiovascular adverse events.
    The potential for therapeutic doses of triptans to constrict human coronary arteries is small, but not absent.

    Fatal cardiovascular events reported within one day:
    19 out of 5 million patients/100 million attacks
    SC: 4/11 (3675) had contraindications
    10/11 (972) had 1 or more risk factors
    PO: 1/8 (137) had contraindications
    5/8 (632) had 1 or more risk factors

11. Adolescent migraines evolve very quickly and often require faster acting formulations, i.e., intranasal.

12. Menstrual migraines respond favorably to mini-prevention with longer acting agents:
    a. Amerge ½ 2.5 mg q. 6 hours (maximum 5 mg/day)
    b. Zomig 25 mg q. 6 hours (maximum 10 mg/day)
    c. Frova 2.5 mg q. 8hrs (maximum 7.5 mg/day

13. The observed proportion with birth defects (n=12) for total births with any trimester of exposure (n=243) from the Sumatriptan pregnancy register 1/1/96 through 4/30/00 is 4.92 and the registry of findings does not suggest a greater risk of birth defects among the prospectively reported pregnancies compared with that of the general population.

14. Stroke risk in migraineurs <u>under</u> age 45
    no migraine: 5-10/ 100,00 women/year
    migraine 3X: migraine with aura 6X;
    migraine plus OC's 5-17X
    migraine plus OC's plus smoking: 34X
    no Δ stroke risk with triptan added

15. Prophylactic treatments in pregnancy
    C → propanolol, topiramate, gabapentin, calcium channel blockers, doxepin
    D → divalproex sodium, amitriptyline, nortriptyline
    X → phenytoin, ergotamine, valproic acid

16. Acute treatment in pregnancy
    B → acetaminophen, NSAI's meperidine, methadone, morphine, prednisone, Metoclopramide
    C → caffeine, butorphanol, codeine, propoxphene, butalbital, dexamethasone, Chlorpromazine, haloperidol, prochlorperazine, triptans
    D → benzadiazepine
    In 3rd trimester: NSAI, narcotics, butalbital

SPECIFIC ANTIMIGRAINE ABORTIVE AGENTS

DRUG	IMITREX (SUMATRIPTAN)	ZOMIG (ZOLMITRIPTAN)	AMERGE (NARATRIPTAN)	MAXALT (RIZATRIPTAN)	AXERT (ALMOTRIPTAN)	FROVA (Frovatriptan Succinate)	Relpax (eletriptan hydrobromide)	MIGRANOL (DIHYDROERGOTAMINE)
Manufacturer	Glaxo	Zeneca	Glaxo	Merck	Pharmacia	Elan	Pfizer	Novartis
Administered	PO, SC, IN	PO, IN	PO	PO	PO	PO	PO	IN
Strenth and Dosage	Oral: 25 mg, 50 mg, 100 mg Injectable: 6 mg Intranasal: 10 mg, 20 mg	Oral: 2.5 mg, 5.0 mg IV: 5.0 mg	1 mg 2.5 mg	Oral: 5mg, 10mg Disiteg: 5 mg, 10 mg	6.25 mg 12.5 mg	2.5 mg	20 mg 40mg	4 mg
Bio-Availability	Oral: 15% Injectable: 97% Intranasal: 17%	40%	70%	45%	70%	20%	50%	32%
Time to Peak plasma concentration (T-MAX)	Oral: 2-2 1/2 hrs. Injectable: 12 mins. Intranasal: 1hr.	Oral: 2 hrs IV: 3hrs	2-3 hrs.	Oral: 1-1 1/2 hrs. Disinteg: 1 1/2-2 1/2	1-3 hrs	2-4 hrs.	1.5-2.0 hrs	30-60 mins
Elimination Half-Life	Oral: 1 1/2 hrs. Injectable: 2 hrs. Intranasal 2 hrs.	Oral and IN: 3hrs - 2-3 hrs. for active metabolic (2-6 x more potent)	6 hrs	Oral: 2-3 hrs	3-4 hrs	26.0 hrs.	6 hrs.	7-9 hrs
Plasma Protein Binding	18%	25%	30%	14%	35%	15%	85%	93%
Excretion	Urine: 60 % Feces: 40%	Urine: 60 % Feces: 30%	Urine	Urine: 82% Feces: 18%	Urine: 75 %	Urine: 32% Feces: 62%	90% Urine	Feces
Dose	Oral: 25-100 mg; may repeat in 2 hrs.; up to 200mg q.d. Injectabble: 6 mg; may repeat in 1 hr. up to 2 q.d. Intranasal: 20 mg; may repeat in 2 hrs; up to 40 mg q.d.	2.5 mg; may repeat in 4 hrs.; up to 10 mg q.d.	2.5 mg; may repeat in 4 hrs.; up to 5 mg q.d.	5-10mg; may repeat in 2 hrs; up to 30 mg q.d.	12.5 mg; may repeat in 2 hrs.; up to 25 mg q.d	2.5 mg; may repeat in 2 hrs.; up to 7.5 mg qd	20-40mg:may repeat in 2 hrs; max 80mg/day; 80mg-most effective but moderate increased side effects	One spray (0.5 mg) per nostril; may repeat in 15 mins; up to 4 sprays (2 mg) total in 24 hrs.

	TRIPTANS	MIGRANAL
CONTRAINDICATIONS:	Ischemic heart disease - angina, history of MI Prinzmetal - variant angina Uncontrolled hypertension Hemiplegic or basilar migraine	
	* MAO inhibitor - within 2 weeks * Ergot type medications * Methysergide (Sansert) within 24 hours * Used in pregnancy only if potential benefits justify risks to fetus (Category C)	* Sumatriptan * Ergot-type medications * Methysergide (Sansert) within 24 hours * Known peripheral arterial disease * Sepsis; following vascular surgery * Pregnant or nursing mothers (Category X)
POTENTIAL DRUG INTERACTIONS:	SSRI's-rare reports of weakness/incoordination *use 5 mg Maxalt with Inderal only *Relpax-do not use within 72 hrs with potent CYP3A4 inhibitors: Ketoconazule (nizoral), itraconazule (sporanox) nefazodone (serazone), troleandromycin (jaul) clarithromycin (biaxine), ritonavir (norvir) and nelfinavir (viracept). Zomig - ↑ 1/2 life 2 X with Cimetidine	* Vasoconstrictors: increased BP * Beta blockers: theoretical increase * Vasoconstrictive effects * Nicotine: increased vasoconstrictive effects * Macrolide antibiotics (erythromycin and troleandomyein): increased vasospasm * SSRIs: same
SIDE EFFECTS:	Flushing, tingling, feeling of tightness	Rhinitis, nausea, dizziness, vomiting, altered sense of taste

DRUGS FOR MIGRAINE PROPHYLAXIS

DRUG	AMITRIPTYLINE (ELAVIL)	NADOLOL (CORGARD)	VERAPAMIL (CALAN SR)	DIVALPROEX SODIUM (DEPAKOTE ER)	GABAPENTIN (NEURONTIN)	METHYSERGIDE (SANSERT)	TOPIRAMATE (TOPAMAX)
INITIAL DOSE: **MAXIMUM DOSE:** **FREQUENCY:**	10 mg 300 mg 1/day	20 mg 320 mg 1/day	120mg 480 mg 1/day	250 mg 2000 mg 1/day	300 mg 4800 mg 3-4/day	2 mg 8 mg 4/day	25 mg 100 mg 2/day
STRENGTHS	10, 25, 50, 75, 100, 150 mg	20, 40, 80 mg	120, 180, 240 mg	250, 500 mg	100, 300, 400, 600, 800 mg	Available in Canada 2 mg	25, 100 mg tabs 15, 25 mg Sprinkle Caps
SIDE EFFECTS	Dry mouth Sedation Sexual dysfunction Urinary retention Weight gain	Bradycardia Depression Fatigue Impaired sex Memory Impairment Sleep disorder	Constipation Edema Elevated LFTs	Drowsiness Nausea Hair loss Tremor Weight gain Elevated LFT's	Dizziness Lethargy Unsteadiness Swelling	Cramps Drowsiness Ecema Coolness of extremities GI symptoms Weight gain	Weight loss Sedation Cognitive Fatigue Paresthesias
CONTRA-INDICATION	MAO inhibitor Acute MI Angle closure glaucoma	Asthma Diabetes CHR Depression Raynaud's disease	Constipation Heart block Some arrhythmias	Liver disease Pregnancy		CV disease Vascular disease Pregnancy Severe HTN Collagen disease Impaired liver/kidney function Over 6 months continuously	Kidney stones
DRUG INTERACTIONS	Elavil levels increased by quinidine, cimetidine, some SSRI's, phenothlazines, type 1-C antiarrhythmics (propafenone, flecainide)	↓ B/P with reserpine, ↑ Haldol levels by cimetidine, chlorpromazine ↑ levels by Dilantin, PHB, rifampin	Caution with Verapamil Levels of digoxin, Tegretol, Theophylline are ↑	↓ by Dilantin, Tegretol, PHB ↑ by aspirin Absence status with clonazepam ↑ Dilantin, Valiym, Lamictal, PHB May ↑ unbound friction of tolbutamide and Coumadin	Decreased by Maalox	↑ Beta blockers peripheral ischemia	↓ Digoxin ↓ BCPs Avoid diamox
RELATIVE INDICATIONS	Sleep promotion Depression Chronic pain states	Angina Essential tremor Hypertension Tachycardia	Angina Hypertension	Epilepsy Bipolar	Epilepsy Chronic neuropathic pain Restless legs Tremor		Tremor Bipolar Neuropathic pain Epilepsy

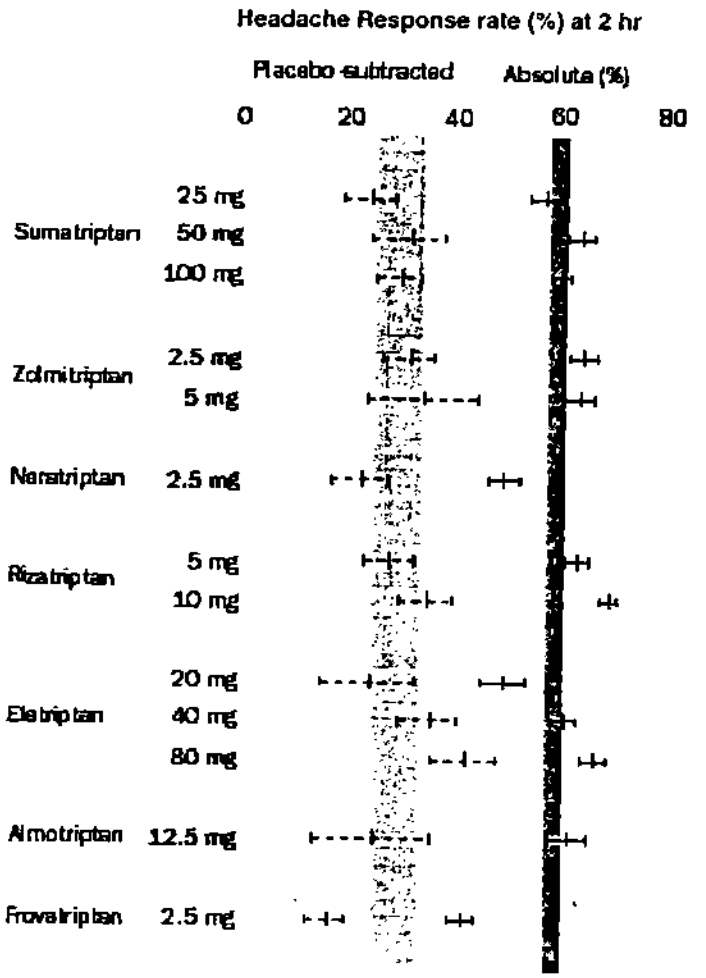

Figure 1 Headache response at 2 hours. (Reprinted with permission from *Lancet*.[7])