MIGRAINE:	AGENTS FOR ACUTE TREAT	TMENT	Prepared by	: L Regier BSP, B Jensen BSP, S Downey BSP © www.f	RxFiles.ca S	ept 13
Generic/ TRADE PREGNANCY CATEGORY	INDICATIONS and CONTRAINDICATIONS (CI)	SIDE EFFECTS (SEs)	DRUG (DI) INTERACTIONS	COMMENTS	DOSING ↓↓ usual; MAX/24hr	\$ per 6 doses
Naratriptan AMERGE,g (1,2.5mg D shaped tab);otc n uk)	1 st line for mod & severe attacks ◆ ≤40% of all attacks & 25% of all patients do not respond ¹ ; high recurrence rate (~40% @24 _{hr} IMITREX)	For all: (13 trials suggest no differences) 65 Chest discomfort or tightness <7% (or tightness of neck/throat); {Actual CV events extremely rare if low CV risk}.	•Serotonin syndrome (e.g. agitation, excitement, hypomania, myoclonus, tremor, hyperreflexia, ataxia, motor	Selective 5HT-1 receptor agonists ^{2hr} response: NNT=2.4 Take at the earliest onset of migraine pain best, but taking during aura phase may be too early. If failure with one, can try another fast vs slow; route	1mg or 2.5mg; may repeat in 4h MAX=5mg/24h	50 generic /104
Rizatriptan MAXALT,g (5,10mg capsule shaped tab; 5,10mg wafer,g oral dissolving)	•cardiac or cerebrovascular disease (or high risk for the same); risk of MI -1/5,000,000 migraine attacks treated 2.49 •hypertension uncontrolled; PVD; ?diabeles	nausea, facial flushing, tingling & paresthesia; CNS: dizziness<10%, fatigue, somnolence; poor taste Suma; Suma SC burning @ site	weakness, fever/chills, diarrhea) with concurrent MAOIs, SSRIs, TCAs or lithium. MAOIs = stop at least 2 weeks prior to triptans (except Nara,	Triptan + NSAID: benefit some? Frecurence use 2 x w/k Frequent triptans use can cause rebound & chronic daily headache (Some clinicians suggest 10-18 doses/month ok NIHB ▼Max: 12/month; lack of data²) Less nausea vs DHE but ↑ recurrence rate	5mg or 10mg; may repeat in 2h MAX 20mg/24h If With Propranolol: 5mg; 10mg/24hr	42 generic /107 age >6yrFDA USA: 15mg/24hr
Sumatriptan IMITREX,g (25,50,100mg DF tab;	•hemiplegic or basilar migraine <u>Caution</u> : decrease dose/avoid •↑CV risk: e.g. ♂>40yrs; ♀>50yrs; smoker	Differences generally not clinically significant; trends: •Almo/Nara/Frova⇔less SEs slow onset •Riza⇔more recurrence?	Almo & Frova); caution with others Do NOT use within 24hr of DHE, other ergot preps or other	SC IMITREX ⁴ {most effective triptan form @2hr: NNT=2; OK if nausea; but less convenient & ^cost; useful for cluster type HA or allemate rapid triptan e.g. Zolmig nasal}	50-100mg <u>PO</u> ; 25-50mg may repeat in 2h (MAX 200mg/24h)	54generic /105
-generic 25,50 & 100mg tabs 5,20mg Nasal spray; 6mg/0.5ml SC inj); [50mg OTC in the UK; Sumavel DosePro	Renal dysfunction with nara/suma Hepatic dysfn with all triptans Sulfa allergy?: Almo/Elet/Nara/Suma Aspartame	•Zolmi⇔more adverse effects? •Suma = 50mg dose often as effective as 100mg & as well tolerated as 25mg³	triptans (risk of additive vasoconstriction/ coronary vasospasm) •↑level of Zolmi use ≤ 5mg/24h	SC best bioavailability/fastest onset -10-15min versus <u>orals</u> onset 30 - 120min; (nasal also fast! 15min) Nasal IMITREX ^{& DF} (age >12yr ⁵), MAXALT Wafer, &/OR ZOMIG RAPIMELT or masal 4 may be preferred if	5mg or 20mg in <u>one</u> <u>nostril</u> ; may rpt in 2h (MAX 40mg/24h) 6mg <u>SC</u> ; may rpt x1in	103 210generic
6mg/5ml: needle-free inj in USA; Treximet in USA, Suma 85mg + naproxen 500mg] Zolmitriptan	EDS Criteria:Treat migraine headache (Age >18yr)	• baseline cardiac evaluation/ECG recommended for \$>40yr & \$\forall >50yr	with cimetidine, propranolol, ciprofloxacin & fluvoxamine	• fast relief required nasal -15min; melt tab 30min; & • nausea &/or vomiting present {wafer/melt: can take without water & inconspicuous}	1h; (MAX 12mg/24h) 1.25mg or 2.5mg;	/290 38generic
(2.5mg tab: 2.5mg	• Eletriptan RELPAX,g X ⊗:20-40mg tab, • Almotriptan AXERT g ▼ '6.25-12.5mg tab • Frovatriptan FROVA X ⊗: 2.5mg; may rep. ?less effective but less recurrence \$99/6 doses. (N.	may rpt x1 in 2hr; similar to po sumatript to beat after 2hr, MAX 5mg/24hrs; long t½=:	tan; \$799 ^{/93} /6dose. age≥12yr ^{FDA/CDN} 25hr; <mark>slower</mark> onset ^{90320min} arting 2days prior to onset of period.}	AMERGE ⁴ - slower onset ^{60-120min} but •better tolerability, less drug interactions •longest duration, lowest recurrence rate [2.5mg less effective?: at 2hr vs riza 10mg & at 4hr vs suma 100mg] ⁶⁵	may repeat after 2hr MAX 10mg/24h With Propranolol ↓ zolmi dose. 5mg nasal	/98 192
Dihydroergotamine DHE MIGRANAL/g (1mg/ml injectable) (4mg/ml nasal spray - 0.5mg/spray) NOTE: pump 4Xs into the air to prime nasal spray for 1st use.		Metoclopramide MAXERAN, REGLAN alone sometimes effective Chest discomfort, tingling & paresthesia, nausea, drowsiness, dizziness, diarrhea, muscle cramp. May cause/worsen Raynaud's. Nasal spray = rhinitis, taste disturbance but ↓ nausea • baseline cardiac evaluation/ECG recommended for ♂>40yr & ♀>50yr	•Do NOT use within 12hr of triptans or 24hrs for naratriptan ⁶ (risk of additive vasoconstriction/ coronary vasospasm) •↑ toxicity (eg. severe ischemia) of ergot preps with potent CYP 3A4 inhibitors: clarithromycin, erythromycin,	■Non-selective 5HT agonist: (also α, β & DA) ■More nausea than triptans but less chest pain ■May precede with 10mg metoclopramide, or prochlorperazine 5-10mg esp. if severe attack requiring repeat doses or if nausea present ■IV = rapid onset but more adverse effects so reserve for severe attack (IV dihydroergotamine 5 days more effective than shorter ≤2day courses; effect up to 4wks.¹55) ■SC = slower response rate vs IMITREX but longer acting & lower recurrence rate at 24hr Nasal spray = response rate similar to oral triptans, or nasal IMITREX'; low recurrence rate **Time Time Time Time Time Time Time Time	0.5-1mg q1h SC, IM or IV; repeat q1h to Max 3mg/24h ^{6mg/wk} {IV Img/50ml over ≥15min Refractory: 11.25mg total IV over 5day ¹⁵⁵ 1 spray into <u>each</u> nostril stat; repeat in 15 minutes prn MAX 4 spray/attack; 6 sprays/24h (8 sprays/wk)	\$ 44 per 1 pkg (3 bottles X4 doses per bottle)
Ergotamine/ X v caffeine (1/100 tab ^c) CAFERGOT Ergodryl, Ergomar SL & Cafergot-PB Supp – D/C'd by the company.	2 nd line due to ↓ efficacy & ↑ toxicity CI •cardiac or cerebrovascular dx or risk factors, uncontrolled BP, ?diabetes, pregnancy/breastfeeding •hemiplegic or basilar migraine Caution: renal/hepatic dysfunction	Chest discomfort/ pain, tingling & paresthesia, nausea, vomiting, dizziness, drowsiness, diarrhea, muscle cramps. May cause/worsen Raynaud's. Chronic daily headache (with overuse; limit to 1-2 days/week)	propranolol, protease inhibitors & itra-, posa- & vori-conazole. •Sibutramine:↑ risk of serotonin syndrome. • p -porphyria concern	Non-selective 5HT agonist Most nausea of all abortive preps; recent meta- analysis?'s efficacy as mainly appeared to ↑ N&V ⁸ Ergotism with overuse: vasoconstriction ⇒ numbness, tingling, paresthesia, blue hands/feet, (gangrene of extremities), HA, seizures, abdominal/chest pain, lack of pulse	2 tab po stat, then 1 tab Q30-60min, MAX 6tab/24h;10/wk	13
NSAIDs ASA, high dose, diclofenac K+Cambia powderx o, lbuprofen, Naproxen (s00mg Tab or Supp*) NSAIDs P:PsL ASA, high dose, diclofenac K+Cambia powderx o, lbuprofen, Naproxen (s00mg Tab or Supp*)	Treatment of mild-moderate attack CI •hypersensitivity to ASA/NSAID (ie bronchospasm, nasal polyps) Caution: CV/renal dx; ↑GI ulcer risk { buprophen 400mg: NNT=3-4. Cochrane Rev Useful also for tension-type headache}	GI irritation/upset/bleed, dizziness, fatigue, rash Renal impairment esp. if CrCl <30ml/min See also NSAIDs chart for other drugs/formula	• ↑ bleeding with warfarin & antiplatelet agents • May blunt effect of some antihypertensives • others • May displace DVA & older ations. In only on the statement of the state	Overuse (ie >10-15x/wk) can lead to rebound headache or medication-induced headache for short-term, intermittent use; will increase effectiveness if used together with triptan	ASA 650-1300mg po q4h X2 Ibuprofen 400-800mg po q4-6h X2 (MAX 3.2g/24h) ANAPROX 275-550mg po q4-6h X2 (MAX 1.65g/24h) Naproxen 500-1000mg po "Consider suppository if vomiting	(MAX 4g/24h) \$1 \$1 OTC 400m; \$ 15 (MAX 1.5g/24h) \$2 OTC 220mg
292s, TYLENOL #3, PL FIORINAL X &, others Acetaminophen TYLENO	Treatment of mild-moderate attack if: •not relieved with simple analgesics •vasoconstrictors are contraindicated DL	constipation (esp. with codeine); {Opioids may ↑ risk of chronic HA}	Products with ASA similar to above Additive effects with other CNS depressants	Overuse associated with rebound & medication induced headache (esp. caffeine combos); for short-term & intermittent use Dependency potential omask pain without affect	1-2 tabs/caps stat: may repeat 3-4h prn MAX 6-8 tabs/caps per ing 24h	T3=\$ 8 292= \$ 8 Fc½= \$ 20
Butorphanol X & 10mg/ml nasal spray (previous STADOL) Img/spray	Reserve for rescue treatment or when DHE/triptans ineffective or contraindicated	Drowsiness, dysphoria, nausea & vomiting, nasal irritation (Dose ~ 1mg/spray)	•↑ CNS depression: CNS depressants, MAOIs, alcohol	Dependency potential Mixed agonist-antagonist so can precipitate withdrawal in persons addicted to opiates		\$60 (15 doses)
Other/Adjunct: metoclopramid metoclopramid	e MAXERAN 10-20mg SC/IV q8h {IV: in 50ml over ≥15min } \$5-10mg PO	◆chlorpromazine 5-25mg IV (10-25mg PO) q4-6h (IV: p	oretreat with \geq 500ml NS} \bullet domperidone 20-30	unlikely to be "safer" than others ⁹ ; ⇔ patient selection & cc ong PO (or 60mg PR) lid-qid <mark>◆ prochlorperazine</mark> or 100 to 10	dexamethasone 4-10mg IV x1; 8-24mg PC	D x1

*trimebutine MODULION 200mg cap pox1 (may \taup Tryptan efficacy with less nausea & photophobia. 48) *haloperidol MULDOL 5mg IV in 500ml normal saline or 5mg IV over 3mins *diphenhydramine*

Migraine headache: consider if recurrent severe disabling headache assoc. with nausea & sensitivity to light & a normal neurological exam. Characteristically is unilateral 60%, ?asymmetrical, pulsating, builds up over minutes to hours, & aggravated by routine physical activity.

Generic/ PREGNANCY	AGENTS FOR PROPHYLAXIS INDICATIONS AND	most ↓ # of days &/or frequency of attacks	DRUG (DI)	COMMENTS	DOSING	\$
Generic/ PREGNANCY CATEGORY	CONTRAINDICATIONS CI	SIDE EFFECTS	INTERACTIONS	COMMENTS	range / typical	/mon
Amitriptyline ELAVIL/g (10, 25, 50,75* mg tab) Nortriptyline AVENTYL/g (10,25mg cap)	1st line especially if associated depression, chronic pain, insomnia, & tension-type headache {fluoxetine possibly effective in some.} CI •severe cardiac, kidney, liver, prostate or thyroid disease; glaucoma,	Anticholinergic: dry mouth, constipation, etc.; dizziness, drowsiness , postural hypotension, ↑weight (high drop out rate _200% with amitriptyline) Nortriptyline ⇔less drowsiness, dry mouth & weight gain than	Avoid with MAOI, cisapride, clonidine ↑ adverse effects for MAOI, anticholinergics, other CNS depressants ↑ effect with CCBs, SSRIs cimetidine,phenothiazines,	•Central neuromodulator of noradrenaline & serotonin (5HT) system •Start low & titrate up to help ↓ side effects; may give single dose at bedtime {nortriptyline ~1.5-2x more potent than amitriptyline; less side effects, but also less trial evidence}	10-25-150mg/d 50mg po hs 100mg po hs 10-150mg hs 50mg po hs	
Metoprolol LOPRESOR/g (25°,50°,100°mg/tab,SR100,200mg) Timolol BLOCADEN PL	hypotension •seizures •MAOI use 1st line option (especially in patients age <60, or those with hypertension or CVD) Can reduce frequency and some	amitriptyline; but less evidence Fatigue, bradycardia, hypotension, coldness of extremities, depression, impotence, sleep disturbance,	cipro (↓ TCA metabolism) ↑ levels of rizatriptan (↓ dose of riza to 5mg) ↑ risk of peripheral ischemia with ergots ↑ cardiovascular effects	•Caution in elderly ⇒ anticholinergic effects •Modulation of central catecholaminergic system & brain serotonin •May be class effect however β-blockers with intrinsic sympathomimetic activity may not be	100mg po hs <u>Metopr</u> 50-200mg/d 50mg po bid 100mg SR po od <u>Timolol</u> 10-30mg/d	
(5 ⁵ ,10 ⁵ ,20 ⁵ mg tab) / g Propranolo INDERAL/ g (10 ⁵ ,20 ⁵ ,40 ⁵ ,80 ⁵ & 120 ⁵ mg tab; LA 60,80,120,160mg)	CI •asthma, heart block or uncompensated heart failure, peripheral vascular disease	bronchospasm	with CCBs, clonidine ↑ levels of β-blocker with cimetidine, fluoxetine Altered hypo-glycemic effect with sulfonylureas	effective (data from small/poorly designed trials) ¹⁰ •Atenolol 50.150mg/day & Nadolol 80.240mg/day also used. •Start low & titrate up q1-2 weeks •If failure with one→ may try another β-blocker •Taper slowly before stopping to prevent rebound	10mg po bid 9 Propran 80-320mg/d Initial: 20mg bid 80mg po bid 120mg LA po od	10-1
Flunarizine SIBELIUM /g (Smg cap) Discontinued Verapamil	↓frequency; <u>little effect</u> on intensity or duration. Tolerance may develop.	Flunarizine: fatigue, weight gain, depression, parkinson like side effects (EPS) Verapamil: bradycardia,	† effect of CNS depressants Verapamil = many DIs (CYP 3A4 inhibitor). ASA, barbs, β-blockers, carbamazepine, cimetidine, digoxin,	•? modulate transmitters rather than vasodilation •Maximum effect may take several months •Overall benefit similar to β-blockers •Verapamil often used but less studied	5-10mg/d 5mg po hs (>6yrs old) 10mg po hs starting dose 240-320mg/d	
ISOPTIN, others (120,180°,240°SR tab/cap)	<u>Caution</u> : β-blockers, Parkinsons <u>Verapamil</u> ~1 st line option expert opinion	hypotension, constipation , nausea, edema, headache	erythromycin, ketoconazole, lithium, statins & theophylline	•Verapamil good prophylaxis→ cluster headache [Flunarizine seldom used/discontinued (grobably effective in kids ⁵);]	240mg SR po od (higher doses in cluster HA?)	
Divalproex (DVA) EPIVAL/g (125,250,500mg EC tab;1000mg/10ml vial ^X ⊗	1 st line for severe migraine (↓ severity, duration; ↓ \(\lambda_{\infty}\sigma	DVA: Common: nausea lst 6mo, tremor, wt gain, alopecia, ↑LFTs, drowsy, diarrhea (transient, best if start low & titrate up) dizziness; polycystic ovary. Rare: ↓	↑ ASA & warfarin effect ↑ Valproic acid level by: ASA, cimetidine, erythromycin, fluoxetine, isoniazid & salicylates ↓ Valproic acid level by: carbamazepine, cholestryramine,	Anticonvulsants: effective NNT=3.8.AE's common se⇒DCNNNH-2433 19 • Divalproex less GI effects than valproic acid (Divalproex 250mg OD x7d, then 250mg BID x7d, then 250mg AM+500mg HS x7+d) • Monitor LFTs initially: if ↑ enzymes, then ↓ dose; if 2-3x normal→stop drug; Mech: Modulation of GABA receptors?	500-1500mg/d 125mg po bid cc 250mg po bid-tid cc 500mg bid cc with meals	
Gabapentin NEURONTIN (100, 300, 400mg cap) (600°,800°mg tab ▼↑\$)	migraine with vertigo topiramate 50mg/day CI • liver disease	platelets (\psi dose helps) & WBC, hepatotoxic, skin rx's, pancreatitis, hyperammonemia.	lamotrigine, phenobarbital, phenytoin, primidone, rifampin & topiramate Valproic acid ↑'s levels of: amitriptyline, carbamazepine epoxide	Gabapentin ?? ineffective @ <2,400mg/day 20, Cochrane (Gabapentin & Topiramate are Peds options – see antiepileptic chart for dosing)	{Initiate:300mg tid} 600-800mg po tid	
Topiramate TOPAMAX 25,50,100,200mgtab; 15, 25mg sprinkle cap)	Caution: children → hepatotoxicity Monitor: CBC, Platelets, LFT (Level 350-830 umol/1 – trough) -see comments column & antieoileutics chart p 8:	Neural tube defects Pregnancyspina bifida 1-2%. Suicidal ideation NNH <500 [Topiramate drop-out rate: -30%]	(le. ↑ SE), clonazepam, diazepam, lamotrigine lorazepam, phenobarbital & warfarin	Topiramate ¶ effective 11.12.13.14; 100mg/day equal to propranolol 160mg/day¹5; expensive but generic avail, SE's common (e.g. paresthesias, cognitive, taste, anorexia, fatigue, wtloss). Lamotrigine -ineffective migraine prevention! AAN¹12	{Initiate:25mg po hs, ↑ by 25mg/wk} 50- 100mg po bid {may give 100mg at HS to ↓SE}	
Pizotyline/pizotifen SANDOMIGRAN (0.5mg, DS = 1 ^c mg tab)	2 nd line (seldom used). CI•?diabetes, heart disease, glaucoma, urinary retention, prostatic hypertrophy, renal/hepatic dysfx	Weight gain, fatigue, weak anticholinergic effects	Additive effects with: CNS depressants, anticholinergics	 Serotonin-2 receptor antagonist Somnolence so begin low & dose at bedtime (ie 0.5mg hs). 	Start 0.5mg po hs titrate to 0.5mg tid (or 1.5mg po hs). MAX 6 mg/day	1n
Methysergide SANSERT (2mg tab 🏔 V)-D/C by Co	3 rd line - for prevention of severe recurrent migraine unresponsive to other agents (seldom used) CI •hypertension, cardiac, liver,kidney, lung & collagen dx; þ .porphyria concern. •thrombophlebitis & pregnancy	Retroperitoneal, cardiac & pulmonary fibrosis ⇒ do not use for >6 months duration without weaning & a 1-2 month drug holiday! Nausea, muscle cramps, weight, ↓hair, claudication, hallucinations	•Do NOT use within 24hr of triptans (risk of ↑ vasoconstriction/spasm) ↑ toxicity of ergots with: clarithromycin, erythromycin, propranolol & protease inhibitors	 Serotonin-2 receptor antagonist with carotid vasoconstrictor effect Active metabolite If no effect after 3 week trial, not likely to help Taper dose over 2-3 weeks before stopping! 	2-8mg/d 2mg po bid cc 2mg po tid cc	

OTHER: candesartan ATACAND 16mg/day Norway trial; (or lisinopril 20mg/day), venlafaxine EFFEXOR XR75mg – 150mg/day (similar to TCAs, less evidence, less anticholinergic); Coenzyme Q10 75mg BID -100mg TID. ◆Acupuncture?¹¹³; Spinal manipulation riboflavin Vit B2 400mg/d \$10, magnesium citrate ~500mg/d\$10, feverfew TANACET considered ineffective, butterbur (petasites) extract PETADOLEX ≤ 75mg bid 16 ◆BOTOX inj 25-155 IU ~q3mon¹7, CDN¹1/FDA¹10? (for chronic daily HA & chronic migraine but NOT chronic tension or episodic migraine). Journal 15 HA days/mol NSAIDs: some evidence for benefit with naproxen na+; ✓ mensrual migraine. Frovatriptan intermittent for prevention of menstrual migraine: used q12h short-term starting 2days prior to onset of period.

PROPHYLACTIC THERAPY should be considered if: ◆ migraines severe enough to impair quality of life or patient has ≥ 3 severe attacks per month which fail to respond to abortive therapy.

TIPS: ◆use one agent at a time ◆start low & titrate up; once effective dose reached, continue for minimum 3 month trial to evaluate effectiveness (benefits usually seen after 1-2 months) ◆ efficacy depends on withdrawal of analgesics causing rebound or chronic daily headache ◆if refractory to single agent, may try dual therapy (eg. beta blocker + TCA) if refractory; consider neuro consult if no response ◆continue effective tx for 9-12mon or indefinitely if severe/recurrence; discontinue gradually to prevent rebound ◆before NSAID/triptan consider metoclopramide or domperidone ◆in some ♀ long cycle continuous birth control pills can help ↓ migraines but may avoid Ocs if aura (Yrisk).

Success of prophylaxis considered to be ↓ in severity or frequency of headache by 50% ◆reassess in teens (eg nearly 40% of teens sep if no migraine family history, no longer had headaches 10 yrs later Monastero 2006)

Approach to Migraine: Considerations

- may consider metoclopramide or domperidone 1st; NSAID and/or triptan also recommended first line;
 - in very severe attacks, SC sumatriptan likely to be most effective & rapid; consider need for rapid onset vs recurrence, GI tolerance of po form, etc.
 - Link to Review Article in AFP Feb 2011: http://www.aafp.org/afp/2011/0201/p271.html
- PROPHYLAXIS: 1st line: beta-blockers (propranolol, metoprolol), TCAs, valproic acid, topiramate.
- MENSTRUAL Related Migraine (MRM): severity may be increased; duration of headache may be longer and may be harder to treat than regular migraine
 - may consider NSAID or triptan for short-term treatment, several days before and during menstruation 20

Agents not effective or too many side effects:

*SSRIs, clonidine, methylsergide, oxcarbazepine, melatonin

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