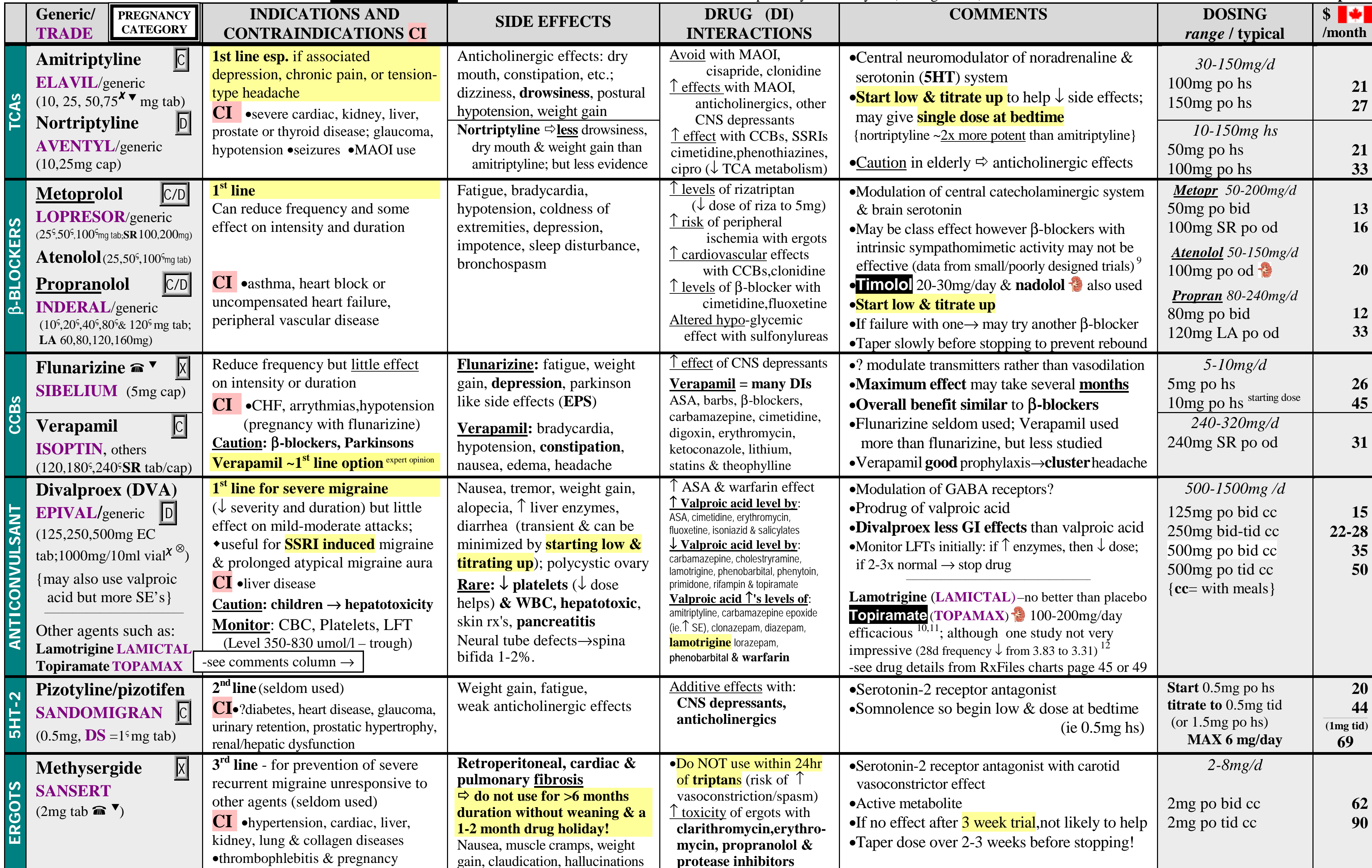
	Generic/ TRADE (PREGNANCY CATEGORY)	INDICATIONS and CONTRAINDICATIONS (CI)	SIDE EFFECTS	DRUG (DI) INTERACTIONS	COMMENTS	DOSING usual; MAX/24hr	$ per 6 doses
TRIPTANS	**Naratriptan** C **AMERGE** ☎ ▼ (1,2.5mg D shaped tab)	**1st line for severe attacks** ◆ ≤40% of all attacks & 25% of all patients do not respond [1]; high recurrence rate (~40% @24hr IMITREX) **CI** •cardiac † or cerebrovascular disease (or risk factors for same) (risk of MI ~1/5,000,000 migraine attacks treated [2]) •uncontrolled hypertension •?diabetes •hemiplegic or basilar migraine **Caution: decrease dose/avoid** •Renal dysfunction with nara/suma •Hepatic dysfn with all triptans •aspartame ZOMIG Rapimelt, MAXALT wafer ⇨caution in PKU pts ☎ **EDS Criteria**:Treat migraine headache (Age >18 or <65)	**For all:** † Chest discomfort or tightness (or tightness of neck/throat) facial flushing, tingling & paresthesia, nausea **Riza / Zolmi** ⇨ dizziness, fatique, somnolence (8-10%) **Suma / Nara** ⇨ sulfa allergy ? **Differences generally not clinically significant; trends**: •Nara = less adverse effects? •Zolmi = more adverse effects? **•Suma = 50mg dose appears as effective as 100mg & as well tolerated as 25mg**[3] ◆ **baseline cardiac evaluation/ECG recommended for ♂ >40yr & ♀ >50yr**	•**Serotonin syndrome** (e.g. agitation, excitement, hypomania, myoclonus, **tremor**, hyperreflexia, ataxia, motor weakness, fever/chills, diarrhea) **with concurrent MAOIs, SSRIs, TCAs or lithium.** MAOIs = stop at least 2 weeks prior to triptans (except Nara); caution with other agents **•Do NOT use within 24hr of DHE**, other **ergot** preps or other **triptans** (risk of additive vasoconstriction/ coronary vasospasm) •↑ levels of **Zolmi** (use ≤5mg/24h) with **cimetidine,ciprofloxacin & fluvoxamine**	•Selective 5HT-1 receptor agonists **•Effective any time during an attack but the sooner the better**; for **SC IMITREX** taking during aura phase may be too early **•If failure with one, can try another** **•Frequent use of triptans can result in rebound & chronic daily headache** (MAX weekly/monthly dose? Some clinicians suggest 12-18 doses per month; no supporting data[2]) •Less nausea vs DHE but ↑ recurrence rate **SC IMITREX** [4] •**best bioavailability/fastest** onset ~15min versus oral onset 30 – 120min **Nasal IMITREX, MAXALT Wafer, &/OR ZOMIG RAPIMELT** [4] may be preferred if • **fast relief required** ~15min • **nausea &/or vomiting present** **AMERGE** [4] **- slowest onset but** **•better tolerability, less drug interactions** **•longest duration** **•lowest recurrence rate**	1mg or **2.5mg**; may repeat in 4h **MAX=5mg/24h**	**104**
	Rizatriptan C **MAXALT** ☎ ▼ (5,10mg capsule shaped tab; 5,10mg **wafer**)					5mg or 10mg; may repeat in 2h **MAX 20mg/24h** With Propranolol: 5mg; 15mg/24hr	**103**
	Sumatriptan C **IMITREX** ☎ ▼ (25,50,100mg **DF tab**; 5,20mg **Nasal spray**; 6mg/0.5ml **SC inj**)					**50**-100mg PO; may repeat in 2h (**MAX 200mg/24h**)	**104**
						5mg or **20mg** in one nostril; may rpt in 2h (**MAX 40mg/24h**)	**104**
						6mg SC; may rpt x1in 1h; (**MAX 12mg/24h**)	**289**
	Zolmitriptan C **ZOMIG** ☎ ▼ (2.5mg tab; 2.5mg **ZOMIG Rapimelt** tab)	◆**Almotriptan AXERT** ☎⊗:6.25-12.5mg tab may repeat x1 in 2hr; similar to po sumatriptan; $100/6 doses. ◆**Frovatriptan FROVA** ✗ ⊗: 2.5mg; may repeat after 2hr, MAX 3tabs/24hrs; long t½, ? less effective but less recurrence; Approved by FDA, but **not yet available in Canada**: {Review:Med Letter Feb02}				1.25mg or **2.5mg** ; may repeat after 2hr **MAX 10mg/24h** With Propranolol ↓ zolmi dose	**103**
ERGOTS	**Dihydroergotamine DHE** X **MIGRANAL**/generic (1mg/ml **inj**) (4mg/ml **nasal** spray) NOTE: pump 4Xs into the air to prime nasal spray for 1st use.	**1st line agent for severe & ultra-severe attacks** (for status migrainosus, pre-dose antiemetic, e.g. **metoclopramide**, x2-3 days) ⇨ **CI** •cardiac or cerebrovascular disease(or risk factors);uncontrolled hypertension, ?diabetes, pregnancy •hemiplegic or basilar migraine **Caution**: renal/hepatic dysfunction	Metoclopramide **MAXERAN, REGLAN** alone sometimes effective Chest discomfort, tingling & paresthesia, nausea, drowsiness, dizziness, diarrhea, muscle cramp 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**[5] (risk of additive vasoconstriction/ coronary vasospasm) •↑ **toxicity** (eg. severe ischemia) of ergot preps: with **clarithromycin, erythromycin, itraconazole, propranolol, & protease inhibitors**	•Non-selective 5HT agonist **•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[5] •**SC** = slower response rate vs IMITREX but longer acting & lower recurrence rate at 24hr [6] •**Nasal spray** =response rate similar to oral triptans, or nasal IMITREX[5]	0.5-**1mg** q1h **SC**, IM or IV;repeat q1h **to MAX 3x/24h** {IV 1mg/50ml over ≥15min	**32**
						1 spray into each **nostril** stat;repeat in 15 minutes prn **MAX 4 spray/attack; 8 sprays/24h**	**$ 39** per 1 pkg (3 bottles X4 doses per bottle)
	Ergotamine/ ✗ ▼ X **caffeine** (1/100 tab$, supp) **CAFERGOT**	**2nd line** due to ↓ efficacy & ↑ toxicity **CI** •cardiac or cerebrovascular disease(or risk factors),uncontrolled hypertension, ?diabetes, **pregnancy** •hemiplegic or basilar migraine **Caution**: renal/hepatic dysfunction	Chest discomfort/ pain, tingling & paresthesia, nausea, vomiting, dizziness, drowsiness, diarrhea, muscle cramps CAFERGOT-PB Supp & ERGOMAR SL – DC'd by manufacturer		•Non-selective 5HT agonist **•Most nausea of all abortive preps;** recent meta-analysis ?'s efficacy as mainly appeared to ↑ N&V[7] **•Overuse associated with ergotism** (vasoconstriction with numbness, tingling, paresthesia, gangrene of the extremities, headaches, convulsion, and abdominal & chest pain) **and chronic daily headache**	2 tab SL stat, then 1 tab Q30-60min, **MAX** 6tab/24h;10/wk	**11**
	Ergotamine/ ✗ ✆ X **caffeine/diphenhydramine ERGODRYL** 1/100/25 cap					1 cap PO stat (MAX 4cap) then repeat Q30min; **MAX** 6cap/24h;10/wk	**13**
NONSPECIFIC ANALGESICS	**NSAIDs** C/D B/D ie high dose **ASA, ibuprofen, naproxen** Na+ or **naproxen** K+ **ANAPROX** ✗ ▼	**Treatment of mild-moderate attack** **CI** •hypersensitivity to ASA/NSAID (ie bronchospasm, nasal polyps) **Caution**: if cardiovascular or renal disease; GI ulcer risk.	•GI irritation/upset/bleed, dizziness, fatigue, rash •Renal impairment esp. if CrCl <30ml/min	•↑ bleeding with **warfarin & antiplatelet agents** •Displaces DVA & older **sulfonylureas** so↑ toxicity •May blunt effect of some antihypertensives •others	•**Overuse (ie >3x/wk) leads to rebound headache & to medication-induced chronic daily headache**; for short-term & intermittent use •Enteric ASA too slow. Buffered ASA OK •Fast acting (e.g. **ANAPROX**) may be useful	**ASA** 650-1300mg po q4h X2 (**MAX 4g/24h**) **Ibuprofen** 400-800mg po q4-6h X2 (**MAX 3.2g/24h**) **ANAPROX** 275-550mg po q4-6h X2 (**MAX 1.65g/24h**)	**$ 1** **$ 1** OTC 200mg **$ 15**
	Combo analgesics C (**292s, TYLENOL #3, FIORINAL** ✗ ✆,others)	**Treatment of mild-moderate attack if**: •not relieved with simple analgesics •vasoconstrictors are contraindicated acetaminophen TYLENOL ▼ B : doses of ~1gram sometimes effective if taken early	Drowsiness, dysphoria, nausea, constipation (esp. with codeine)	•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** ◆may mask pain without affecting underlying pathophysiology	1-2 tabs/caps stat: may repeat 3-4h prn **MAX 6-8 tabs/caps per 24h**	**T3=$ 7** **292= $ 8** **Fc½= $ 15**
	Butorphanol ✗ ✆ C 10mg/ml **nasal spray** (previous **STADOL**)	**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	1 spray in 1 nostril; may repeat in 3-5hr **MAX 16 sprays/24h**	**$55** (15 doses)

† CORONARY VASOSPASM POTENTIAL: still greatest concern; recent metaanalysis showed no clinically important differences between agents therefore one unlikely to be "safer" than others [8]; ⇨**patient selection & counseling** important!

ADJUNCT AGENTS: ◆**metoclopramide** 10mg SC/IV {IV: 10mg /50ml over ≥15min}; 5-10mg PO ◆**chlorpromazine** 5-25mg IV (10-25mg PO) q4-6h {IV: pretreat with ≥ 500ml NS} ◆**domperidone** 10-40mg PO (or 60mg PR) tid-qid ◆**prochlorperazine** STEMETIL 5-10mg IV (25mg PR) q8h

MIGRAINE: AGENTS FOR **PROPHYLAXIS**

Prepared by S Downey BSP, L Regier BSP, B Jensen BSP - www.RxFiles.ca Sept 04



	Generic/ TRADE	PREGNANCY CATEGORY	INDICATIONS AND CONTRAINDICATIONS CI	SIDE EFFECTS	DRUG (DI) INTERACTIONS	COMMENTS	DOSING *range* / typical	$ /month
TCAs	**Amitriptyline** **ELAVIL**/generic (10, 25, 50,75✗▼ mg tab) **Nortriptyline** **AVENTYL**/generic (10,25mg cap)	C D	**1st line esp.** if associated depression, chronic pain, or tension-type headache **CI** •severe cardiac, kidney, liver, prostate or thyroid disease; glaucoma, hypotension •seizures •MAOI use	Anticholinergic effects: dry mouth, constipation, etc.; dizziness, **drowsiness**, postural hypotension, weight gain **Nortriptyline** ⇨less drowsiness, dry mouth & weight gain than amitriptyline; but less evidence	Avoid with MAOI, cisapride, clonidine ↑ effects with MAOI, anticholinergics, other CNS depressants ↑ effect with CCBs, SSRIs cimetidine,phenothiazines, cipro (↓ TCA metabolism)	•Central neuromodulator of noradrenaline & serotonin (**5HT**) system •**Start low & titrate up** to help ↓ side effects; may give **single dose at bedtime** {nortriptyline ~2x more potent than amitriptyline} •Caution in elderly ⇨ anticholinergic effects	*30-150mg/d* 100mg po hs 150mg po hs *10-150mg hs* 50mg po hs 100mg po hs	 21 27 21 33
β-BLOCKERS	**Metoprolol** **LOPRESOR**/generic (25ς,50ς,100ςmg tab;**SR** 100,200mg) **Atenolol** (25,50ς,100ςmg tab) **Propranolol** **INDERAL**/generic (10ς,20ς,40ς,80ς& 120ς mg tab; **LA** 60,80,120,160mg)	C/D C/D	**1st line** Can reduce frequency and some effect on intensity and duration **CI** •asthma, heart block or uncompensated heart failure, peripheral vascular disease	Fatigue, bradycardia, hypotension, coldness of extremities, depression, impotence, sleep disturbance, bronchospasm	↑ levels of rizatriptan (↓ dose of riza to 5mg) ↑ risk of peripheral ischemia with ergots ↑ cardiovascular effects with CCBs,clonidine ↑ levels of β-blocker with cimetidine,fluoxetine Altered hypo-glycemic effect with sulfonylureas	•Modulation of central catecholaminergic system & brain serotonin •May be class effect however β-blockers with intrinsic sympathomimetic activity may not be effective (data from small/poorly designed trials)[9] •**Timolol** 20-30mg/day & **nadolol** (renal) also used •**Start low & titrate up** •If failure with one→ may try another β-blocker •Taper slowly before stopping to prevent rebound	***Metopr*** *50-200mg/d* 50mg po bid 100mg SR po od ***Atenolol*** *50-150mg/d* 100mg po od (renal) ***Propran*** *80-240mg/d* 80mg po bid 120mg LA po od	 13 16 20 12 33
CCBs	**Flunarizine** ☎▼ **SIBELIUM** (5mg cap) **Verapamil** **ISOPTIN**, others (120,180ς,240ς**SR** tab/cap)	X C	Reduce frequency but little effect on intensity or duration **CI** •CHF, arrythmias,hypotension (pregnancy with flunarizine) **Caution: β-blockers, Parkinsons** **Verapamil ~1st line option** expert opinion	**Flunarizine:** fatigue, weight gain, **depression**, parkinson like side effects (**EPS**) **Verapamil:** bradycardia, hypotension, **constipation**, nausea, edema, headache	↑ effect of CNS depressants **Verapamil = many DIs** ASA, barbs, β-blockers, carbamazepine, cimetidine, digoxin, erythromycin, ketoconazole, lithium, statins & theophylline	•? modulate transmitters rather than vasodilation •**Maximum effect** may take several **months** •**Overall benefit similar** to **β-blockers** •Flunarizine seldom used; Verapamil used more than flunarizine, but less studied •Verapamil **good** prophylaxis→**cluster** headache	*5-10mg/d* 5mg po hs 10mg po hs starting dose *240-320mg/d* 240mg SR po od	 26 45 31
ANTICONVULSANT	**Divalproex (DVA)** **EPIVAL**/generic (125,250,500mg EC tab;1000mg/10ml vialχ⊗) {may also use valproic acid but more SE's} Other agents such as: **Lamotrigine LAMICTAL** **Topiramate TOPAMAX**	D	**1st line for severe migraine** (↓ severity and duration) but little effect on mild-moderate attacks; •useful for **SSRI induced** migraine & prolonged atypical migraine aura **CI** •liver disease **Caution: children → hepatotoxicity** **Monitor**: CBC, Platelets, LFT (Level 350-830 umol/l – trough) -see comments column →	Nausea, tremor, weight gain, alopecia, ↑ liver enzymes, diarrhea (transient & can be minimized by **starting low & titrating up**); polycystic ovary **Rare: ↓ platelets** (↓ dose helps) **& WBC, hepatotoxic**, skin rx's, **pancreatitis** Neural tube defects→spina bifida 1-2%.	↑ ASA & warfarin effect **↑ Valproic acid level by**: ASA, cimetidine, erythromycin, fluoxetine, isoniazid & salicylates **↓ Valproic acid level by**: carbamazepine, cholestryramine, lamotrigine, phenobarbital, phenytoin, primidone, rifampin & topiramate **Valproic acid ↑'s levels of**: amitriptyline, carbamazepine epoxide (ie.↑ SE), clonazepam, diazepam, **lamotrigine** lorazepam, phenobarbital & **warfarin**	•Modulation of GABA receptors? •Prodrug of valproic acid •**Divalproex less GI effects** than valproic acid •Monitor LFTs initially: if ↑ enzymes, then ↓ dose; if 2-3x normal → stop drug **Lamotrigine** (**LAMICTAL**)–no better than placebo **Topiramate** (**TOPAMAX**) (renal) 100-200mg/day efficacious[10,11]; although one study not very impressive (28d frequency ↓ from 3.83 to 3.31)[12] -see drug details from RxFiles charts page 45 or 49	*500-1500mg /d* 125mg po bid cc 250mg bid-tid cc 500mg po bid cc 500mg po tid cc {**cc**= with meals}	 15 22-28 35 50
5HT-2	**Pizotyline/pizotifen** **SANDOMIGRAN** (0.5mg, **DS** =1ςmg tab)	C	**2nd line** (seldom used) **CI**•?diabetes, heart disease, glaucoma, urinary retention, prostatic hypertrophy, renal/hepatic dysfunction	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**	20 44 (1mg tid) 69
ERGOTS	**Methysergide** **SANSERT** (2mg tab ☎▼)	X	**3rd line** - for prevention of severe recurrent migraine unresponsive to other agents (seldom used) **CI** •hypertension, cardiac, liver, kidney, lung & collagen diseases •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 gain, 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	 62 90

NON-PHARMACOLOGICAL AGENTS: **riboflavin** (Vit B2) 400mg/day, **magnesium** 400-600mg/day, **feverfew TANACET** 125mg/d. •**BOTOX injection** – effective (~q3mons[13]) for some pts (renal) =↓ dose for renal dysfunction

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 prophylactic 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 single agent ineffective, may try a **combination** (eg beta blocker + TCA); consider neuro consult if no response •continue effective therapy for **9-12 months; discontinue gradually** to prevent rebound • **Success of prophylaxis** considered to be **↓ in severity or frequency of headache by 50%**

CI =contraindication **CNS**=central nervous system **DI**=drug interaction **LFT**=liver function test **SE**=side effect **SR**=sustained release **$**=total cost Sask. χNon-formulary in SK ☎EDS status SK ▼covered NIHB ⊗not NIHB ✗prior NIHB ς =scored tab

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