MOOD STABILIZERS & ADJUNCT AGENTS

Generic/Form **TRADE** g=generic avail.	SIDE EFFECTS	MONITOR Q6-12 Months	COMMENTS/ DRUG LEVEL	DRUG INTERACTIONS	INITIAL & MAX DOSE	USUAL DOSE RANGE	$ /100day
Carbamazepine(CBZ) **TEGRETOL** g (100ᶜ,200ᶜ mg chew tab) (200ᶜ,400ᶜmg CR tab) (200ᶜmg tab) (20mg/ml susp) P1,P2-3 L Pregnancy category→ Malformation <5% ? cleft palate, spina bifida OR=2.6, but baseline 1:1000. ↑↑ with DVA. Folic acid 5mg/d 3mo prior & 1st trimester, then 0.4-1mg/day.	**Common**: GI N/V, drowsy, dizzy, **unsteady**, pruritic **rash<10%** may cross react with phenytoin & phenobarb; **↓WBC** dose related, **CR tab: less SE** GI/CNS. **Rare**: aplastic anemia, **↑ liver enzymes**, heart abnormalities, ↓ serum sodium/Vit K, SLE, exfoliative dermatitis, ocular effects, **↓WBC** (persistent 2%), ↓ T3/T4, alopecia, Asian & HLA-B* 1502; Caucasian & HLA-A* 3101: ↑↑risk skin rx. **WEIGHT GAIN = minimal**	CBC,Platelets, TSH,LFT, Lytes, **Level** ECG for pts >45yrs	√ BPAD -acute mania, rapid cycle, **mixed** & prophylaxis √ trigeminal neuralgia, seizures Option for **aggressive** patients & those with **neurologic dx**. CI: **hepatic**/ porphyria **dx**; safe in renal dx **17-54 umol/l** Wait until after auto-induction phase (4wks)! Less DI with oxcarbazepine than CBZ	**↑ Carbamazepine level by:** cimetidine, **clarithro/erythromycin, danazol, diltiazem, felodipine**,**fluoxetine**, **fluvoxamine**, grapefruit juice, isoniazid, ketoconazole, **lamotrigine**, metronidazole, nefazodone, phenobarbital, **propoxyphene**, ritonavir,**verapamil** & valproate **↓ Carbamazepine level by:** phenytoin,phenobarb,St.Johns wort,theophylline **Carbamazepine ↓levels of**: Valproate **INDUCES P450 3A4 System**^	200mg hs 1800mg/day (**autoinduction** of P450 system complete in 4 weeks; may start low-dose & ↑ weekly x4 weeks; also ↓'s SE. Wait ~ 4 wks for levels.)	200mg po bid 200mg CR bid 200mg po tid 400mg po bid 400mg CR bid 600mg po hs **800mg po hs**	24 36 33 42 64 33 **42**
Divalproex (DVA) **EPIVAL** g (125,250,500mg EC tab); 1000mg/10 ml vial ✗⊗) P L **-prodrug** of VPA; see **valproic acid below**	**Common**: nausea, diarrhea, dizzy, ataxia, somnolence, sedation, **tremor**, fatigue, confusion, headache, abdominal cramps, hair loss often reversible, menstrual disturbances **Rare: ↓platelets & WBC, hepatotoxic**, skin rx's,**pancreatitis**,neural tube defects 1-2% **Caution: polycystic ovaries** **WEIGHT GAIN= ++** (up to 59%, more common in ♀; mean ↑ of **8-14kg**) Pregnancy registry: heart defect & spina bifida 10.7 vs 2.9% in control gp. ↑malformations with valproate Artama 05. esp >1g/d Perucca 05. Folic acid 5mg/d 3mo prior & 1st trimester, then 0.4-1mg/day. May↓IQ in newborn. Concern1st trimester.	CBC,Platelets, LFT **Level**	√ BPAD **acute mania,rapid cycle, mixed, prophylaxis** & depression √ seizures & migraine prophylaxis; Option for aggression; Safe in renal dx. Acute Mania -Oral load of 20mg/kg has been used CI: **hepatic dx** & kids≤2yr **400-700 umol/l**	**↑ Valproic acid level by:** aspirin, cimetidine, erythromycin, felbamate, fluoxetine, isoniazid, salicylates **↓ Valproic acid level by:** carbamazepine, cholestryramine, lamotrigine, meropenem,phenobarbital,phenytoin,rifampin,ritonavir **Valproic 2C9 acid ↑ levels of**: amitriptyline, carbamazepine epoxide (ie.↑ SE), clonazepam, diazepam,ethosuximide,**lamotrigine,** lorazepam, phenobarbital**,** TCAs, **warfarin** **Not ↓ effect of BCP's**	250mg od 3000mg/day Mainly an enzyme **inhibitor**	250mg po bid 250mg po tid **500mg po bid** 1gm po hs 500mg po tid	45 64 **83** 83 120
Lamotrigine **LAMICTAL** g (25ᶜ,100ᶜ,150ᶜ mg tab; 5ᶜmg chewable tab) (2mg chewable tab✗▼) P L Not teratogenic in animal, but ↑ risk of fetal death. ↑ non-syndromic oral cleft. Pregnancy: ↓level & ↑level in breast milk. ↑↑ risk if with DVA.	**Common:** dizzy, nausea, vomiting, asthenia, headache, somnolence, ataxia, ↑ alertness, diplopia, abdominal pain, rash **Rare**:**Stevens-Johnson Sx** #, 1st 2months, <0.1% & toxic epidermal necrolysis, hepatotoxic, leukopenia, aseptic meningitis & tics in kids **WEIGHT GAIN= neutral effect**	CBC,LFT	√ seizures; Option: Alt./adjunct **for BPAD I for acute depression** & **Bipolar II for rapid cycling** FDA Jun03 **Rash** 10% →life threatening 0.3%# (If drug related/severe, D/C at first sign of rash) 4-39umol/l (? Sig/not routinely avail.) Breast feeding: caution b/c of rash	**↑ Lamotrigine level** by: sertraline, **valproate** **↓ Lamotrigine level** by: **BCP's, carbamazepine, phenytoin**, phenobarb, primidone, rifampin, ritonavir NO EFFECT on P450 enzymes **Rarely ↓ effect of BCP's & folic acid**	25mg hs ↑ only **25-50mg/week** increments 400mg/day	50mg po bid **100mg po bid** 150mg po bid **If using with valproate:** 25mg hs start↑12.5mg/wk 100mg po hs Mono Therapy dose 50-400mg/d; 50-200mg/d with **divalproex**	65 **122** 177 22 65
Lithium carbonate **CARBOLITH** g DURALITH (150,300,600mg cap; 300mg SR tab LITHMAX⊗) **PMS-LITHIUM CITRATE** (300mg/5ml **syrup** ✗▼) P1,P2-3 L Ebstein's anomaly0.1% Fetal echo at ~18 wks gest.	**Common:** nausea/vomiting/diarrhea, edema, **polyuria**, **polydypsia**, , ↑WBC, alopecia, acne, psoriasis, hypothyroidism, hyperparathyroidism, monitor for toxicity, ↑ Ca⁺⁺,↑ K⁺ & **tremor** propranolol or ↓ Lithium dose helps **Level 1.5-2 mmol/l:** drowsy, ataxia, slurred speech, hypertonicity, tremor dose related,Tx Inderal **Level >2mmol/l:** arrhythmias, ↓ heart rate, myocarditis, seizures, coma & death. **WEIGHT GAIN= +** (25-60% -mean gain **7.5kg**)	CBC,TSH, ECG Urinalysis, Lytes, Ca⁺⁺ **SCr**, **Level Trough** 8-12hr**:** ~0.8-1.1mmol/L (in elderly 0.4-0.7 mmol/L)	√ BPAD FDA ≥12yr: **acute mania & prophylaxis, mild depression Suicide reduction** for BPAD pts Option:Cluster headache, OCD, antidepressant augmentation & aggression Safe to use in **liver dx** CI: **↓renal fx**, **breast feeding** caution Acute Mania **0.8-1.2 mmol/l** Maintenance Tx **0.6-1.0 mmol/l** (Li+DVA or Li) >DVA Balance BPAD I relapse prevention	**↑ Lithium level by:** ACE inhibitors, ARBs,carbamazepine, Ca channel blockers, diuretics, fluoxetine, metronidazole, NSAIDS not ASA, sodium depletion, spironolactone, **↓ Lithium level by**: caffeine, metamucil, NaCl, theophylline, topiramate **Lithium↑ toxic** by ↑ serotonin effect: l-tryptophan, MAOI's, sibutramine, verapamil With **Antipsychotics**- ↑ neurotoxicity	300mg hs 1800mg/day Maintain consistant salt (Na⁺) diet!	300mg po hs 300mg po bid 300mg SR bid ⊗ 600mg po hs 300mg po tid 300mg SR tid ⊗ **900mg po hs** 1200mg po hs	27 31 76 37 36 104 **36** 40
Valproic acid -VPA **DEPAKENE** g (250mg cap; 500mg EC cap; 250mg/5ml **syrup**) P L	As per **divalproex above** **Depakene generally has more GI** side effects than **Epival**	CBC,Platelets, LFT **Level**	Divalproex & valproic acid are **not** interchangeable medications As per **divalproex above**	As per **divalproex above** Pregnancy registry: heart defect & spina bifida 10.7vs2.9% in control gp. ↑ malformations with valproate Artama 05, esp >1g/d Perucca 05. Folic acid 5mg/d 3mo prior & 1st trimester, then 0.4-1mg/day. May ↓ IQ in newborns.	250mg od 3000mg/day	250mg po bid **500mg po bid** 1gm po hs 500mg po tid	47 **121** 121 179
Gabapentin **NEURONTIN** g (100,300,400 cap) (600ᶜ,800ᶜmg tab ✗▼↑cost) P L	**Common**: somnolence, dizzy, ataxia, nystagmus, n/v, blurred vision, tremor, slurred speech, rash, behavioral changes in kids & ↓WBC. **WEIGHT GAIN= +** (appears dose related), euphoria; ?akathisia on withdrawal	NA **little effect as mood stabilizer**	√seizures; Option:Neuropathic pain &**Anxiolytic in severe Panic dx & social phobia**,↓ dose if ↓ renal fx, 3-25umol/l (? Significance/avail.)	Antacids ↓ by 20% absorption NO other signif. interactions With doses >600mg less is absorbed since mechanism is saturated	100mg hs (↑ **100**-400mg/day increments) 3600mg/day	100mg po bid 300mg po bid **400mg po bid** 300mg po tid	39 83 **100** 124
Topiramate **TOPAMAX** g (25,50,100,200mg tab; 15, 25mg sprinkle cap) P L Hypospadias in male infants. Cleft lip/palate.	**Common**: nausea, dizzy, tremor, ataxia, somnolence, **cognitive dysfunction**, headache, paresthesias, sedation, fatigue, diarrhea, metabolic acidosis, **nephrolithiasis & glaucoma** acute angle, stop Tx! **WEIGHT GAIN= loss possible** (seems dose & duration dependent & > in ♀) **Renal stones**1.5% thus try to ↑ **fluid intake**	CNS SE synergize with agents such as divalproex	Weight loss ~**4kg** ?dose related May minimize weight gain induced by other psychotropics √ seizures; 80% Renal elimination √ migraine prophylaxis + dva→ ↓ platelet&↑ **encephalopathy**	**↓ Topiramate level** by: **carbamazepine** & phenytoin (40%), valproate (15%) **↑ toxicity** of topiramate with: Ketogenic diet; Aceta-,dor-& metho-zolamide (topiramate has carbonic anhydrase inhib. properties) **Topiramate** >200mg/d **↓ effectiveness** : **BCPs** birth control pills	25mg hs ↑ only by **25-50mg/week** increments **250-400**mg/day	25mg po bid 50mg po bid **100mg po bid** 200mg po bid 400mg po hs Caution: **↓ sweating** especially in children	103/283 220/538 190/512 275/751 275/751 generic/Trade

=↓ dose for renal dysfx ς=scored ☎ =Exception Drug Status Sask ✗ =Non formulary in Sk ▼covered NIHB **CI**=contraindication **CR**=control release **Dx** =disease **EC**=enteric coated **SE**=side effect **SR**=sustained release ^ **Carbamazepine ↓ level of**: alprazolam, aripiprazole, bupropion, clonazepam, cyclosporine, dexamethasone, diazepam, doxycycline, ethosuximide, felodipine, fentanyl, irinotecan, lamotrigine, haloperidol, nefazodone, nevirapine, **OC'S**, phenytoin, phenobarbital, phenothiazines, pregnancy tests, **risperidone**, steroids, theophylline, triazolam, tricyclics, valproate, voriconazole & **warfarin**.

Pregnancy: Most have teratogenic risk, risk > if multiple meds; try for monotherapy &↓serum level. Try to avoid in 1st trimester. Consider antipsychotic, benzodiazepine, ECT or ?lithium. Initiate folate 5mg/d, 3mo pre-conception, & 1st trimester, then 1mg/d.

√ **Useful for/in # Rash:** ↑dose, ↑too quickly, if with valproic or in kids → ↑rash rate. **Clonazepam/Lorazepam** (0.5-2mg qid)/**antipsychotics** eg. haloperidol, olanzapine✂▼, quetiapine, risperidone, ziprasidone♂, aripiprazole✂♂, asenapine ✂⊗, paliperidone ✗⊗ **acute mania** options.

Drug Induced Mania: abused drugs (alcohol, amphetamines, cocaine, hallucinogens, opiates), antidepressants, baclofen, bromocriptine, captopril, cimetidine, corticosteroids, disulfiram, hydralazine, isoniazid, levodopa, MAOIs, & methylphenidate.

BIPOLAR DISORDER: Overview Of Evidence-based Treatment Guidelines & Options[1,2,3,4,5,6]

MANIA & MIXED STATE

- **Divalproex/valproate: √ mania & mixed** -? use loading dose
- **Lithium: √ mania**
- **Atypical Antipsychotic: √ mania** (esp. for **acute agitation**)
- **Carbamazepine: √ mixed (alternate)** (CBZ can ↓level of DVA, olanzapine & risperidone; thus CBZ not recommended with olanzapine or risperidone) (Oxcarbazepine may be better tolerated than CBZ, but limited clinical evidence)

Combo of Mood Stabilizers: consider if poor response to lithium, DVA or CBZ, severe mania or mixed episodes. Balance (Ensure medication trials are adequate: at least **2weeks** before efficacy can be assessed). Consider other causes: antidepressants, caffeine, alcohol, illicit substances & medical.

Important but select roles:

Benzodiazepines (clonazepam/lorazepam IM/PO): in place or with antipsychotic to **sedate** acutely agitated pt; behavioral control while waiting for mood stabilizer response. Caution resp depression: wait 1-2hrs between IM olanzapine & IM benzo

Antipsychotics: Typical (haloperidol IM/PO): for marked psychosis; rarely as primary antimanic except in exceptional circumstances. may ↑depression

Atypical (risperidone po/M tab/Consta ☕⊗/olanzapine im/po/Zydis ☕▼/ ziprasidone ☾/ aripiprazole ☕☾/ quetiapine/ asenapine ☕⊗/ paliperidone ✗⊗, Sustenna ☕⊗/): acute **mania** option, esp. if marked psychotic Sx; FDA: ≥10yr risperidone/quetiapine & ≥13yr olanzapine/aripiprazole. or in refractory mania. **Disadv**: tardive dyskinesia possible, extrapyramidal Sx, diabetes, ↑weight/lipids & acute dystonias. **Advantage:** rapid onset of action & useful if severe mania

ECT: effective & broad-spectrum; for severe behavioral disturbances/ psychosis marked/suicidality, or if poor combo response, option pregnancy

Less evidence/less preferable options: Gabapentin/lamotrigine/ topiramate/verapamil; **Clozapine** for the truly refractory patient; Experimental: calcitonin, levetiracetam, omega 3 fatty acids, phenytoin & tamoxifen.

RAPID CYCLING (≥4 cycles/year)

- **Divalproex/valproate √ first line**
- **Lithium** or **carbamazepine** √ second line added to DVA if necessary
- **Lamotrigine** (less useful if frequently manic) Risk of life threatening rash ↑'s when combine DVA & lamotrigine.
- ↓ use of antidepressants, nicotine, alcohol & illicit drugs may help

Combination of Mood Stabilizers:
⇨ up to 3 drugs may be used when necessary

Important but limited roles:

Benzodiazepines (clonazepam/lorazepam)

ECT: consider if fail or poor response to combos, an option if pregnant

Less evidence/ less preferable options:
risperidone/**olanzapine**/quetiapine→ but approved in FDA & Canada
gabapentin/topiramate;
verapamil/nimodipine;
clozapine for the **refractory** patient;
thyroxine –less evidence unless **hypothyroid.**

Caution: Antidepressants - particularly TCA's may provoke switch into mania & rapid cycling (switch to mania >10% for TCA vs <5% for SSRI) **Bupropion** less switches than sertraline & much less than venlafaxine Leverich'06

Bipolar DEPRESSION

Frye'11 (assess for risk of suicide/self-harm)

- NNT=10 to ↓ depression sx by at least 50% Van Lieshout'10
- Cognitive-behavioral or interpersonal therapy
- **Lithium √ first line** (may protect against suicide)
- **Lamotrigine √ first line** (esp. to prevent depressive; not great if frequently manic)
- **Quetiapine √ first line** FDA indication Oct/06; 1st line Bipolar II Depression
- **Olanzapine plus SSRI** an option; lurasidone: a 2nd line option
- NOT aripiprazole, gabapentin or ziprasidone monotx or adj levetiracetam
- **ECT**: consider if markedly suicidal, acute psychosis or moderate to severe depression not responding to mood stabilizers/antipsychotics/antidepressants

If non-psychotic: (Switch risk: short illness duration, previous antidepressants & switches)

- Lithium/DVA & antidepressant -often D/C antidepressant after 3-6months (**bupropion,SSRI** ?not paroxetine,SNRI, MAOI, RIMA-**avoid TCA's**) **or**
- Two mood stabilizers (LI & DVA, LI & CBZ, DVA & CBZ) **or**
- Mood stabilizer & **lamotrigine** {Antidepressants may have better outcomes:BPAD II}

If psychotic: (If mood incongruent, may be poorer prognosis than mood congruent)

- Mood stabilizer & antipsychotic **or**
- Mood stabilizer & antipsychotic & antidepressant **or**
- 2 mood stabilizers & antipsychotic

Later treatment options:

- 3 mood stabilizers
- Clozapine for the truly refractory patient
- Other novel treatments: eg. methylphenidate, modafanil & pramipexole

Therapeutic Drug Levels:
Take **trough level** PRIOR to the next dose when steady state is achieved ie. after at least **4-5 days** for carbamazepine & valproic acid. Lithium is often a 12hr trough. (Take any time if suspect toxicity/non-compliance.) Anti-manic levels are not established, thus anticonvulsant levels are used as a guide only. Levels for gabapentin & lamotrigine are not readily avail. (ie. sent to provincial lab) & less known about the significance of a particular level. For CBZ, lithium & valproic acid - levels guide in selecting the correct dose, assessment of pt compliance & avoiding excessive SE.

Continuation/Early Stable Phase:

Acute phase (Duration of **2-10 weeks**) →Medication responder (Euthymia & resolution of Psychosis)
Continuation/Early Stable Phase (Duration of **6-12 weeks**)

Treatment: Pharmacotherapy, **psycho-education** & bio-social rhythm normalization +/- psychotherapy (Cognitive behavioural, interpersonal & remediation in select patients). Beynon '08

- **Mood stabilizer**: maintain optimal serum level, confirm normal lab investigations, ensure no/minimal tolerable side effects, ensure no toxicity
- **Benzodiazepines**: gradual titration to discontinuation if asymptomatic for 2-3 weeks, or continue at minimum doses for Sx management **Disadv:** tolerance, dependence, withdrawal, falls & accidents.
- **Antipsychotics**: gradual titration to discontinuation if asymptomatic for 2-3 weeks, except in persistent or incongruent psychosis, when longer periods are indicated; or continue at minimum doses for Sx management. **Disadv:** tardive dyskinesia,extrapyramidal Sx, akathisia, diabetes, weight gain & acute dystonias. Gardner CMAJ 2005
- **Antidepressant**: gradual titration to discontinuation if asymptomatic for 6-12 weeks, or continue at minimum doses for Sx management (Taper over a ≥2-4week period)
- **ECT**: possible continuation/maintenance ECT (weekly to monthly ECT) is indicated for patients who respond poorly to continuation medications or prefer ECT.

Abruptly stopping pharmacotherapy provokes relapse; thus **if possible, D/C gradually over 1 month or more** to prevent relapse.

Maintenance/Prophylactic/Late Stable:

Treatment if medication/prophylaxis (eg. lithium, valproate, lamotrigine limited to prevent mania, aripiprazole mania, olanzapine metabolic SE, quetiapine, risperidone depot mania, & adjunctive ziprasidone mania are first line maintenance options of bipolar disorder), {2nd line: CBZ, paliperidone or combos }, {3rd line: asenapine or combos} CANMAT 2013, but use symptoms & past tx hx to help selection[6]) is acceptable to the pt:

Not recommended: Monotherapy with gabapentin, topiramate or antidepressants; or adjunctive therapy with flupenthixol.

Hx of single episode→Pharmacotherapy, psycho-education & bio-social rhythm normalization, optimally **for 1 year** & preferable not less than 6 months.
Gradual discontinuation over a period of 3 months, but not less than 1 month. Annual monitoring & rapid reassessment where indicated.

Hx of recurrent episodes, or single severe episode & a strong family Hx→**indefinite prophylaxis**,psycho-education & bio-social rhythm normalization +/- psychotherapy. **Adherence** to meds is critical.

Early symptom Exacerbation:

- Optimize mood stabilizer serum level (repeat ~q6months)
- Adjust for change in bioavailability of active agents (e.g. drug interactions etc…)
- Identify & manage substance abuse & caffeine or nicotine intake
- Modify poor sleep hygiene
- Identify & manage psychosocial precipitants or stressors (e.g. adverse life events, negative expressed emotions or hostility in family, new stressors)

If **non responders** then consider other treatments or combos: Mood stabilizers +/-Benzodiazepine for sleep etc. +/-antipsychotic +/-ECT +/-Antidepressants +/-Lamotrigine

Antipsychotics: haloperidol,olanzapine, risperidone, quetiapine etc… √therapeutic use **Adv**=advantage **BZ**=benzodiazepine **CBZ**=carbamazepine **Disadv**=disadvantage **DVA**=divalproex/valproate **ECT**=electroconvulsive therapy **LI**=lithium **Sx**=symptoms

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MOOD STABILIZERS & ADJUNCT AGENTS

Other Sources:

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Health Canada Aug/06 Lamictal warning with non-syndromic oral clefts. Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between LAMICTAL® (lamotrigine) and an increased risk of non-syndromic oral clefts over the reference population for the registry (ie. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, USA)1. Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1,000, as compared to 0.37 per 1000 in the reference population for that registry. The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 3-17. To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/lamictal_2_hpc-cps_e.html

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