

MOOD STABILIZERS & ADJUNCT AGENTS

Generic/ TRADE NAME	SIDE EFFECTS	MONITOR Q6-12 Months	COMMENTS/ DRUG LEVEL	DRUG INTERACTIONS	INITIAL & MAX DOSE	USUAL DOSE RANGE	\$  /100day
Carbamazepine TEGRETOL (100 ⁵ ,200 ⁵ *▼mg chew tab; 200 ⁵ mg tab) (200 ⁵ ,400 ⁵ mg CR tab ☞▼) (20mg/ml susp) 	Common: gastric distress (N/V), drowsy, dizzy, unsteady , pruritic rash , ↓ WBC (dose related) Rare: aplastic anemia, ↑ liver enzymes , cardiac abnormalities, ↓ serum sodium, SLE, exfoliative dermatitis, ocular effects, ↓ WBC (persistent ^{2%}), ↓ T3/T4, alopecia 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 in hepatic dx ; safe in renal dx 17-54 umol/l	↑ Carbamazepine level by: cimetidine, danazol, diltiazem,erythromycin, felodipine,fluoxetine, grapefruit juice, isoniazid,ketoconazole,lamotrigine, metronidazole,nefazodone, phenobarb.,propoxyphene,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 rash rate)	200mg po bid 200mg CR bid 200mg po tid 400mg po bid 400mg CR bid 600mg po hs 800mg po hs	26 52 35 45 97 35 45
Divalproex (DVA) EPIVAL (125,250,500mg EC tab); 1000mg/10 ml vial ^x ☞  -prodrug of VPA; see valproic acid below	Common: nausea, diarrhea, dizzy, somnolence, sedation, tremor, ataxia, fatigue, confusion, headache, abdominal cramps, hair loss, menstrual disturbances Rare: ↓ platelets & WBC , hepatotoxic , skin rx's, pancreatitis ,neural tube defects Caution: polycystic ovaries WEIGHT GAIN= ++ (up to 59%, more common in ♀; mean gain 8-14kg)	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 in hepatic dx 350-830 umol/l	↑ Valproic acid level by: aspirin, cimetidine, erythromycin, felbamate, fluoxetine, isoniazid, salicylates ↓ Valproic acid level by: carbamazepine, cholestyramine, lamotrigine, phenobarbital, phenytoin ,rifampin Valproic acid ↑ levels of: amitriptyline, carbamazepine ^{epoxide} (ie. ↑ SE), clonazepam, diazepam,ethosuximide, lamotrigine , lorazepam, phenobarbital, warfarin Not ↓ effect of BCP's	250mg od 3000mg/day	250mg po bid 250mg po tid 500mg po bid 1gm po hs 500mg po tid	54 78 102 102 149
Lamotrigine LAMICTAL , generic (25 ⁵ ,100 ⁵ ,150 ⁵ mg tab;  5 ⁵ mg chewable tab) (2mg chewable tab ^x ▼) (Not teratogenic in animals, but ↑ risk of fetal death. Pregnancy: ↓ levels & ↑ levels seen in breast milk)	Common: dizzy, nausea, vomiting, asthenia, headache, somnolence, ataxia, ↑ alertness, diplopia, abdominal pain, rash Rare:Stevens-Johnson syndrome # & toxic epidermal necrolysis, hepatotoxic, leukopenia & 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} ↓ dose in renal impairment Rash 10% → life threatening 0.3%# (If drug related/severe, D/C at first sign of rash) 4-39 umol/l (? Significance/not routinely available)	↑ Lamotrigine level by: sertraline, valproate ↓ Lamotrigine level by: BCP's, carbamazepine, phenytoin, phenobarbital, primidone, rifampin NO EFFECT ON Mono Therapy dose 50-400mg/d; 50-200mg/d with divalproex	25mg hs ↑ only 25-50mg/week increments	50mg po bid 100mg po bid 150mg po bid If using with valproate: 25mg hs start 100mg po hs	107 208 299 32 107
Lithium carbonate  CARBOLITH, DURALITH (150,300,600mg cap; 300 ⁵ mg SR tab) PMS-LITHIUM CITRATE  (300mg/5ml syrup ^x ▼)	Common: nausea/vomiting/diarrhea, edema, polyuria, polydypsia , tremor, ↑ WBC, alopecia, acne, psoriasis, hypothyroidism, ↑ ca ⁺⁺ , ↑ K ⁺ 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 ~0.6-1.5mmol/l (in elderly 0.4-0.7 mmol/l)	√ BPAD 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 function,breast feeding Acute Mania 0.8-1.2 mmol/l Maintenance Tx 0.6-1.0 mmol/l	↑ Lithium level by: ACE inhibitors, carbamazepine, Ca channel blockers, diuretics, fluoxetine, metronidazole, NSAIDS, sodium depletion, spironolactone ↓ Lithium level by: caffeine, metacucil, NaCl, theophylline Lithium ↑ toxic by ↑ serotonin effect: l-tryptophan, MAOIs, sibutramine, verapamil With Antipsychotics - ↑ neurotoxicity	300mg hs 1800mg/day	300mg po hs 300mg po bid 300mg SR bid 600mg po hs 300mg po tid 300mg SR tid 900mg po hs 1200mg po hs	29 35 68 35 41 92 41 48
Valproic acid -VPA DEPAKENE  (250mg cap; 500mg EC cap; 250mg/5ml syrup)	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	250mg od 3000mg/day	250mg po bid 500mg po bid 1gm po hs 500mg po tid	69 131 131 193
Gabapentin NEURONTIN , generic (100,300,400 cap)  (600,800mg tablet ^x ▼ ↑cost)	Common: somnolence, dizzy, ataxia, nystagmus, nausea, vomiting, blurred vision,tremor,slurred speech,rash& ↓WBC WEIGHT GAIN= + (appears dose related)	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	53 117 142 177
Topiramate TOPAMAX  (25,100,200mg tab; 15, 25mg sprinkle cap) 	Common: nausea, dizzy, tremor, ataxia, somnolence, cognitive dysfunction , headache, paresthesias, sedation, fatigue, diarrhea, metabolic acidosis, nephrolithiasis & glaucoma. WEIGHT GAIN= neutral/ loss possible (seems dose & duration dependent & > in ♀)	CNS SE synergize with agents such as divalproex Renal stones 1.5% thus try to ↑ fluid intake	Weight loss -4kg ?dose related May minimize weight gain induced by other psychotropics √ seizures; 80% Renal elimination + dva → ↓ platelet&↑ encephalopathy	↓ Topiramate level by: carbamazepine & phenytoin (40%), valproate (15%) ↑ toxicity of topiramate with: Acetazolamide, dorzolamide, methazolamide (topiramate has carbonic anhydrase inhib. properties) Topiramate ↓ effectiveness : oral contraceptive pills	25mg hs ↑ only 25-50mg/week increments 250-400mg/day	25mg po bid 50mg po bid 100mg po bid 200mg po bid 400mg po hs	264 501 476 738 738

☞=↓ dose for renal dysfx ☞=scored ☞=Exception Drug Status Sask ☞=Non formulary in Sk ▼covered NIHBI CI=contraindication CR=control release Dx=disease EC=enteric coated SE=side effect SR=sustained release **Carbamazepine ↓ level of:** alprazolam, bupropion, clonazepam, cyclosporine, dexamethasone, diazepam, doxycycline, felodipine, fentanyl, lamotrigine, haloperidol, **OC's**, phenytoin, phenobarbital, phenothiazines, pregnancy tests, risperidone, steroids, theophylline, triazolam, tricyclics, valproate... & **warfarin**.
Pregnancy: Lithium, carbamazepine, valproic acid have teratogenic risk, risk > if on multiple drugs; thus try for monotherapy & ↓ serum level. Try to **avoid in 1st trimester**. Consider antipsychotics, benzodiazepines, ECT or ?lithium. √ **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 are options in acute mania

BIPOLAR DISORDER: Overview Of Evidence-based Treatment Guidelines & Options^{1,2,3,4}

<p>ACUTE MANIA & MIXED STATE ➡</p> <ul style="list-style-type: none"> ◆ Divalproex/valproate: ✓ mania & mixed -? use loading dose ◆ Lithium: ✓ mania ◆ Carbamazepine: ✓ mixed <p>Combination of Mood Stabilizers: if poor response to lithium, DVA or CBZ then add another agent (at first try not to use DVA & CBZ combinations)</p> <p>Important but limited roles:</p> <p>Benzodiazepines (clonazepam/lorazepam): in place of, or in conjunction with an antipsychotic to sedate the acutely agitated manic patient; behavioral control while waiting for mood stabilizer response</p> <p>Antipsychotics: Typical (haloperidol): for marked psychosis; rarely as sole or primary antimanic agent except in exceptional circumstances. Atypicals (risperidone/olanzapine/quetiapine): efficacious in acute mania, esp. in presence of marked psychotic Sx or in refractory mania. Disadv: tardive dyskinesia, extrapyramidal Sx, diabetes, weight gain & acute dystonias Adv: rapid onset of action</p> <p>ECT: is efficacious & broad-spectrum treatment; consider for severe behavioral disturbances/ marked psychosis, or if poor response to mood stabilizer combinations.</p> <p>Less evidence/less preferable options: Gabapentin/lamotrigine/topiramate/verapamil/nimodipine; Clozapine for the truly refractory patient</p>	<p>RAPID CYCLING ➡ (≥4 cycles/year)</p> <ul style="list-style-type: none"> ◆ Divalproex/valproate ✓ first line ◆ Lithium or carbamazepine ✓ second line added to DVA if necessary <p>Combination of Mood Stabilizers: Up to 3 combos may be used when necessary</p> <p>Important but limited roles:</p> <p>Benzodiazepines (clonazepam/lorazepam)</p> <p>ECT: consider if fail or poor response to various combinations of agents</p> <p>Less evidence/ less preferable options: risperidone/olanzapine/quetiapine } FDA Approved lamotrigine } FDA Approved gabapentin/topiramate verapamil/nimodipine clozapine for the truly refractory patient thyroxine – less evidence unless hypothyroid</p> <p>Caution: Antidepressants - particularly TCA's may provoke switch into mania & rapid cycling (switch to mania >10% for TCA vs <5% for SSRI)</p>	<p>BIPOLAR DEPRESSION ➡</p> <ul style="list-style-type: none"> ◆ Cognitive-behavioral or interpersonal therapy ◆ Lithium ✓ first line ◆ ECT: consider if markedly suicidal, acute psychosis or moderate to severe bipolar depression not responding to mood stabilizers/antipsychotics <p>If non-psychotic:</p> <ul style="list-style-type: none"> ◆ Mood stabilizer & antidepressant (SSRI, SNRI, bupropion, MAOI, RIMA -avoid TCA's) or ◆ Two mood stabilizers (LI & DVA, LI & CBZ, DVA & CBZ) or ◆ Mood stabilizer & lamotrigine/gabapentin <p>If psychotic:</p> <ul style="list-style-type: none"> ◆ Mood stabilizer & antipsychotic or ◆ Mood stabilizer & antipsychotic & antidepressant or ◆ 2 mood stabilizers & antipsychotic <p>Later treatment options:</p> <ul style="list-style-type: none"> ◆ 3 mood stabilizers ◆ Clozapine for the truly refractory patient ◆ Other novel treatments <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>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, lithium & valproic acid. (Take any time if suspect toxicity/non-compliance.) Anti-manic levels are <u>not</u> established, thus anticonvulsant levels are used as a guide only. Levels for gabapentin & lamotrigine are not readily available (ie. sent to provincial lab) & less is known about the significance of a particular level. For carbamazepine, lithium & valproic acid - levels guide in selecting the correct dose, assessment of patient compliance & avoidance of excessive adverse effects.</p> </div> <div style="border: 1px solid black; padding: 5px; margin-top: 10px; text-align: center;"> <p>Abruptly stopping pharmacotherapy provokes relapse; thus if possible, D/C over 1 month or more.</p> </div>
<p>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)</p> <p>Treatment: Pharmacotherapy & psycho-education & bio-social rhythm normalization +/- psychotherapy</p> <ul style="list-style-type: none"> ◆ Mood stabilizer: maintain optimal serum level, confirm normal lab investigations, ensure no/minimal tolerable side effects, ensure no toxicity ◆ Benzodiazepines: gradual titration to <u>discontinuation if asymptomatic for 2-3 weeks</u>, or continue at minimum doses for Sx management ◆ Antipsychotics: gradual titration to <u>discontinuation if asymptomatic for 2-3 weeks</u>, except in persistent or incongruent psychosis, when longer periods are indicated; or continue at minimum doses for Sx management Disadv: tolerance, dependence, withdrawal, falls & accidents. ◆ Antidepressant: gradual titration to <u>discontinuation if asymptomatic for 6-12 weeks</u>, or continue at minimum doses for Sx management (Taper over a 2-4 week period) ◆ ECT: possible continuation/maintenance ECT (weekly to monthly ECT) is indicated for patients who respond poorly to continuation medications or prefer ECT. <p>Maintenance/Prophylactic/Late Stable: Treatment if medication/prophylaxis is acceptable to the patient: <u>Hx of single episode</u> → 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. <u>Hx of recurrent episodes</u>, or single severe episode & a strong family Hx → indefinite prophylaxis, psycho-education & bio-social rhythm normalization +/- psychotherapy.</p>		
<p>Early symptom Exacerbation:</p> <ul style="list-style-type: none"> ◆ Optimize mood stabilizer <u>serum level</u> ◆ Adjust for change in bioavailability of active agents (e.g. <u>drug interactions</u> etc...) ◆ Identify & manage <u>substance abuse</u> & 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) <p>If non responders then consider other treatments or combinations: Mood stabilizers +/-Benzodiazepine for sleep etc. +/-antipsychotic +/-ECT</p>		

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