### MOOD STABILIZERS & ADJUNCT AGENTS

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<td>Carbamazepine (TEGREL)</td>
<td>Common: gastrointestinal distress (N/V), drowsy, dizzy, unsteady, pruritic, rash, WBC abnormalities, rare: aplastic anemia, ↑ liver enzymes, cardiac abnormalities, ↓ serum sodium, SLE, exfoliative dermatitis, ocular effects, ↓ WBC (persistent), ↓ T3/T4, alopecia</td>
<td>CBC, Platelets, TSH, LH, FT, Lutein, Level</td>
<td>↓ BPAD -acute mania, rapid cycle, mixed &amp; prophylaxis</td>
<td>↑ Carbamazepine level by: cimetidine, dextromethorphan, ethanol, felodipine, flucloxetine, grapefruit juice, isoniazid, ketoconazole, lamotrigine, metronidazole, nefazodone, phenobarb, propoxyphene, verapamil, valproate</td>
<td>200mg hs</td>
<td>200mg po bid</td>
<td>26</td>
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<tr>
<td>Divalproex (DVA)</td>
<td>Rare: platelets &amp; WBC, hepatotoxic skin rx's, pancreatitis, neural tube defects</td>
<td>CBC, Platelets, LFT Level</td>
<td>↓ BPAD acute mania, rapid cycle, mixed, prophylaxis &amp; depression</td>
<td>↓ Valproate level by: phenytoin, phenobarbital, St. John's wort, theophylline Carbamazepine level by: polypharmacy Carbamazepine levels of: Valproate INDICATE P450 3A4 System</td>
<td>1000mg/day</td>
<td>1000mg po bid</td>
<td>54</td>
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<tr>
<td>Lamotrigine (LAMICTAL)</td>
<td>Common: dizziness, nausea, vomiting, ataxia, headache, ∆ mood, ∆ alertness, diplopia, abdominal pain, rash Rare: Stevens-Johnson Syndrome &amp; toxic epidermal necrolysis, hepatotoxicity, leukopenia &amp; tics in kids.</td>
<td>CBC, LFT</td>
<td>↓ seizures; Option: Adjunct for BPAD I for acute depression &amp; Bipolar II for rapid cycling</td>
<td>↑ Lamotrigine level by: sertraline, valproate ↓ Lamotrigine level by: BCP's, carbamazepine, phenytoin, phenobarbital, primidone, rifampin</td>
<td>300mg od</td>
<td>300mg po bid</td>
<td>78</td>
</tr>
<tr>
<td>Lithium (CARBOLITH)</td>
<td>Common: nausea/vomiting/diarrhea, edema, polycystic ovaries, tremor, WBC, alopecia, acne, psoriasis, hypothyroidism, ↑ Ca²⁺, ↑ K⁺ Level 1.5-2.0ml2/d: drowsy, ataxia, slurred speech, hypochromic, tremor (dose related) Level &gt;2ml/d: arrhythmias, ↓ heart rate, myocytotoxicity, seizures, coma &amp; death.</td>
<td>CBC, TSH, ECG, Urea, Ca²⁺, SCR, Level</td>
<td>↓ BPAD acute mania &amp; prophylaxis, mild depression Suicide reduction for BPAD pts Option:Cluster headache, OCD, antidepressant augmentation &amp; aggression Safe to use in liver dx CI: ↓ renal function, breast feeding Acute Mania 0.8-1.2ml/m² Maintenance Tx 0.6-1.0ml/m²</td>
<td>↑ Lithium level by: ACE inhibitors, carbamazepine, Ca channel blockers, diuretics, fluoxetine, metronidazole, NSAIDS, sodium depletion, spironolactone ↓ Lithium level by: caffeine, metoclopramide, NaF, theophylline Lithium ↑ toxicity by: serotonin effect: 1-triptophan, MAO's, sibutramine, verapamil With Antipsychotics: ↑ neurotoxicity</td>
<td>1800mg/day</td>
<td>300mg po bid</td>
<td>78</td>
</tr>
<tr>
<td>Valproic Acid (VPA)</td>
<td>As per divalproex above</td>
<td>CBC, Platelets, LFT Level</td>
<td>↓ seizures; Option: Neuruphathic pain &amp; Anxiolytic in severe Panic dx &amp; social phobia, ↓ dose if ↓ renal fx, 3-2.5mg/m²/ (↑ Significance/ avail.)</td>
<td>↑ Valproate level by: carbamazepine &amp; phenytoin (40%), valproate (15%) ↑ toxicity of topiramate with: Acetazolamide, dexamethasone, methotrexate (topiramate has hepatic CYP2C9 induction)</td>
<td>25mg hs</td>
<td>25mg po bid</td>
<td>264</td>
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<tr>
<td>Gabapentin (NEROTIN)</td>
<td>Common: somnolence, dizziness, ataxia, yawning, nausea, vomiting, blurred vision, tremor, slurred speech, rash &amp; ↓ WBC, alopecia, acne, psoriasis, hypothyroidism, ↑ Ca²⁺, ↑ K⁺</td>
<td>NA</td>
<td>little effect as mood stabilizer</td>
<td>Antacids ↓ by 20% absorption NO other significant interactions With doses &gt;600mg less is absorbed since mechanism is saturated</td>
<td>100mg hs (↑ 100-400mg/d increments) 3600mg/d</td>
<td>100mg po bid</td>
<td>264</td>
</tr>
<tr>
<td>Topiramate (TOPAMAX)</td>
<td>Common: dizziness, tremor, ataxia, somnolence, cognitive dysfunction, headache, paresthesias, sedation, fatigue, diarrhea, metabolic acidosis, nephrotoxicity &amp; glaucoma.</td>
<td>CNS SE synergize with agents such as divalproex</td>
<td>Weight loss ↓4kg? dose related May minimize weight gain induced by other psychotropics ↓ seizures; 80% Renal elimination</td>
<td>↓ Topiramate level by: carbamazepine &amp; phenytoin (40%), valproate (15%) ↑ toxicity of topiramate with: Acetazolamide, dexamethasone, methotrexate (topiramate has hepatic CYP2C9 induction).</td>
<td>25mg hs</td>
<td>25mg po bid</td>
<td>700</td>
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</tbody>
</table>

**Generic**

- Carbamazepine
- Divalproex (DVA)
- Lamotrigine
- Lithium
- Valproic Acid (VPA)
- Gabapentin
- Topiramate

**Trade Names**

- Tegretol
- Epival
- Lamictal
- Carbo Lith
- Depakene
- Neurontin
- Topamax

**Side Effects**

- Common: gastrointestinal distress (N/V), drowsy, dizzy, unsteady, pruritic, rash, WBC abnormalities
- Rare: aplastic anemia, ↑ liver enzymes, cardiac abnormalities, ↓ serum sodium, SLE, exfoliative dermatitis, ocular effects, ↓ WBC (persistent), ↓ T3/T4, alopecia
- Weight gain = minimal

**Drug Interactions**

- ↑ Carbamazepine level by: cimetidine, dextromethorphan, ethanol, felodipine, flucloxetine, grapefruit juice, isoniazid, ketoconazole, lamotrigine, metronidazole, nefazodone, phenobarb, propoxyphene, verapamil, valproate
- ↓ Valproate level by: phenytoin, phenobarbital, St. John's wort, theophylline
- Carbamazepine levels of: Valproate

**Usual Dose Range**

- 200mg hs
- 1000mg/day
- 1000mg po bid
- 3000mg od
- 3000mg po bid
- 25mg hs
- 1000mg po bid
- 78 |

**Mainly an enzyme inhibitor**
## BIPOLAR DISORDER: Overview Of Evidence-based Treatment Guidelines & Options

### ACUTE MANIA & MIXED STATE
- Divalproex/valproate: √ mania & mixed -? use loading dose
- Lithium: √ mania
- Carbamazepine: √ mixed

**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)

**Important but limited roles:**
- Benzodiazepines (clonazepam/lorazepam): in place of, or in conjunction with an antipsycotic to sedate the acutely agitated manic patient; behavioral control while waiting for mood stabilizer response

**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

**ECT:** is efficacious & broad-spectrum treatment; consider for severe behavioral disturbances/marked psychosis, or if poor response to mood stabilizer combinations.

**Less evidence/less preferable options:**
- Gabapentin/lamotrigine/topiramate/verapamil/nimodipine; 
- Clozapine for the truly refractory patient

### RAPID CYCLING (
- Divalproex/valproate: √ first line
- Lithium or carbamazepine √ second line added to DVA if necessary

**Combination of Mood Stabilizers:**
- Up to 3 combos may be used when necessary

**Important but limited roles:**
- Benzodiazepines (clonazepam/lorazepam)
- ECT: consider if fail or poor response to various combinations of agents

**Less evidence/less preferable options:**
- Risperidone/olanzapine/quetiapine } FDA Approved
- Lamotrigine  
- Gabapentin/topiramate
- Verapamil/nimodipine
- Clozapine for the truly refractory patient

**Caution: Antidepressants**, particularly TCA’s may provoke switch into mania & rapid cycling (switch to mania >10% for TCA vs <5% for SSRI)

**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

**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

**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:** tolerance, dependence, withdrawal, falls & accidents

**Antidepressant:** gradual titration to discontinuation if asymptomatic for 6-12 weeks, 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.

**Maintenance/Prophylactic/Late Stable:**

Treatment if medication/prophylaxis is acceptable to the patient:

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.

### Early symptom Exacerbation:

- Optimize mood stabilizer serum level
- Identify & manage substance abuse & caffeine or nicotine intake
- 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 combinations: Mood stabilizers +/-Benzodiazepine for sleep etc. +/-antipsychotic +/-ECT

### BIPOLAR DEPRESSION

- 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

**If non-psychotic:**

- Mood stabilizer & antidepressant

**If psychotic:**

- Mood stabilizer & antidepressant
- 2 mood stabilizers & antidepressant

**Later treatment options**

- 3 mood stabilizers
- Clozapine for the truly refractory patient
- Other novel treatments

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**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 not 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.

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