

Bipolar Disorder
Part II
Mood Stabilizers
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- **Introduction**
- **Bible verses**
 - Nahum 1:7 – The Lord is good, a strong hold in the day of trouble; and he knoweth them that trust in him.
 - I Peter 5:7 – Casting all your care upon him; for he careth for you.
- **mood disorders**
 Mood disorders are a group of disorders with depression as an underlying symptom, including major depressive disorder, dysthymic disorder, depressive disorder not otherwise specified (NOS), bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder NOS. Mood disorder can also be caused by a general medical condition.
- **mood stabilizers**
 Neuromodulators (anticonvulsants) and neuroleptics are used to stabilize mood. Below are several with their mechanisms of action and their weight tendencies. Ones with approval are indicated by *.

Selected Neuromodulators/Neuroleptics

NEUROMODULATORS	POSSIBLE EMPHASIS	IONES	NEUROTRANSMITTERS	WEIGHT TENDENCIES
*valproic acid (Depakote)	Mania	Ca NA	↑GABA ↓glutamate	Increase
carbamazepine (Tegretol)	Mania	K NA	↑GABA	Neutral
*Lamotrigine (Lamictal)	Both, but stronger in depression	NA	↓glutamate ↑serotonin	Neutral
gabapentin (Neurontin)	Anxiety	Ca	Possibly ↑GABA or ↓glutamate	Neutral
topiramate (Topamax)	Perhaps both	Ca NA	↑GABA ↓glutamate	Decrease
zonisamide	Perhaps both	Ca NA	SRI DRI ↑GABA, ↓glutamate	Decrease
tiagabine (Gabitril)	Anxiety		GABA reuptake inhibitor GABA RI	Neutral

oxycabazepine (Trileptal)	Mania	K NA	↑GABA	Neutral
levetiracetam (Keppra)	Mania			Neutral
*Geodon	Perhaps both mania and depression		SRI 5HT1A agonist 5HT1D, 5HT2A, 5HT2C antagonist D ₂ antagonist	Neutral
*lithium	Both mania and depression		Modulates the balance between excitatory and inhibitory effects of various neurotransmitters: S, N S reuptake inhibitor Glu, GABA, D and G proteins Inhibits phosphatidylinositol	Increase
*Abilify	Perhaps both mania and depression		D ₂ agonist 5HT1A agonist 5HT2A antagonist 5HT2C antagonist	Neutral
*olanzapine-fluoxetine (Symbyax)	Both mania and depression		olanzapine: D ₂ , 5HT2A, HT2C, 5HT1D fluoxetine: S reuptake inhibitor NE reuptake inhibitor Mild	Increase with Olanzapine

- GABA – An Inhibitory Neurotransmitter
- glutamate – An Excitatory Neurotransmitter
- “Anticonvulsants” that act on calcium channels tend to decrease anxiety.
- “Anticonvulsants” that act on sodium channels tend to stabilize mood.

▪ **mood stabilizers: approved bipolar treatments for depression**

- quetiapine
- olanzapine/fluoxetine

▪ **mood stabilizers: approved bipolar treatments for maintenance**

Mnemonic is “a LOL.”

- aripiprazole
- lithium
- olanzapine
- lamotrigine

▪ **mood stabilizers: drugs approved**

	acute mania/mixed	bipolar depression	bipolar maintenance	adolescent bipolar disorder
lithium	✓		✓	✓
divalproex	✓			

carbamazepine	✓			
lamotrigine	✓		✓	
risperidone	✓			✓
aripiprazole	✓		✓	✓
olanzapine	✓		✓	
quetiapine	✓	✓		
ziprasidone	✓			
olanzapine/fluoxetine		✓ *		

*treatment resistant depression (Symbyax and Abilify)

schizophrenia in adolescence (Abilify and Risperdal)

Drugs may be used for years off-label before they are approved for a specific purpose.

Some are never approved but are effective and continue to be used off-label.

▪ **mood stabilizers: nuances of interest**

general information

- Dates of FDA approval of early mood stabilizers
 - 1970—lithium
 - 1973—thorazine
- Anticonvulsants are the preferred treatment over lithium in certain cases of mood disorders:
 - rapid cycling
 - mixed mania
 - dysphoric mania
 - comorbid substance abuse
- Lorazepam is the benzodiazepine preferred IM in mood disorders because it yields predictable blood levels
- For out-of-control manic episodes an IM neuroleptic (Haldol/haloperidol, Geodon/ziprasidone) is often preferred
- A BMI is often taken before or soon after atypical neuroleptics (except Geodon is sometimes an exception) and sometimes at 4, 8, and 12 weeks; then BMI might be taken quarterly
- Lithium is superior to lamotrigine for mania and lamotrigine is superior to lithium for bipolar depressive episodes
- Quetiapine (Seroquel) is approved for bipolar depression
- Antidepressants are sometimes not given in bipolar disorder in the absence of mood stabilizers and should be discontinued if mania occurs; antidepressants are at times continued 18-30 weeks in non-rapid cycling bipolar I following depression resolution and for 9-17 weeks in rapid cycling
- Stevens-Johnson rash that can occur as a side effect of most anticonvulsant mood stabilizers carries a 10-15% mortality rate. Topamax carries least risk of SJS.
- Drugs approved as mood stabilizers in various stages of bipolar disorders include: lithium, chlorpromazine (Thorazine), atypical neuroleptics (except Clozaril and Invega), carbamazepine XR (Equetro), lamotrigine (Lamictal), and valproic acid (Depakene).

- Rapid-cycling bipolar disorder is four or more episodes in one year; 70% are women; it occurs more with antidepressants and thyroid disease
- Mood stabilizers are potentially teratogenic; anticonvulsants are the most dangerous with an increased risk of 2-3 fold; valproate (Depakote) is the most dangerous in pregnancy (at 1000 mg/day); lamotrigine is the least dangerous of the anticonvulsants in pregnancy
- Anticonvulsants convey increased risk of neural tube defects (spina bifida) in pregnancy; adding folate reduces this risk; valproate has a risk of 1 to 5%; carbamazepine has a risk of .5 to 1%
- High stress during pregnancy results in abnormalities in the HPA axis
- Pregnancy does not necessarily increase mood stability; relapse is increased in bipolar postpartum; the increased relapse risk is 90%
- Lamotrigine (Lamictal), quetiapine (Seroquel), and aripiprazole (Abilify) have antidepressant efficacy
- Inositol has been tried in bipolar disorder; if a mood stabilizer plus an antidepressant fails in bipolar depression, Inositol has been added; Inositol has also been tried in OCD
- Provigil (modafinil) has been tried in bipolar depression
- Asenapine has been tried in bipolar disorder; it has less weight gain

lithium

- 50% of patients are still symptomatic after lithium
- Mechanism of action of lithium
 - lithium is a monovalent cation
 - poor understanding of mechanism of action but actions are broad
 - effects at Inositol monophosphatase
 - effects at phosphoinositol
 - reduces G protein mediated signaling
 - effects on gene transcription
 - effects on ion channels
 - effects on synaptic function
 - effects on secondary messenger systems
 - reduces myoinositol levels and phosphoinositide phosphate
 - the enzyme, glycogen synthase kinase-3, is inhibited, resulting in improvement in neuronal resilience
 - reduces PKC (protein kinase C) activity
 - activation of gene expression for neuronal plasticity growth factor
- Lithium is not metabolized by the liver; 95% is excreted by the kidneys
- Lithium with an 80-90% response rate is the treatment of choice in acute mania and yet, lithium is not as effective in certain states:
 - rapid cycling episodes
 - mixed mania
 - greater than 10 episodes
 - comorbid anxiety or substance abuse disorder
- Lithium with classical antipsychotics has increased risk of certain side effects:
 - extrapyramidal side effects

- neurotoxicity
 - ventricular arrhythmias (with thioridazine/Mellaril)
- Lithium or valproate/Depakote plus an atypical antipsychotic is often the preferred first-line treatment for acute mania
- Thiazide diuretics can decrease plasma sodium and thus, increase lithium reabsorption and increase plasma lithium
- Lithium has low protein binding
- Lithium has an absence of liver metabolism
- Lithium half-life is 17 to 36 hours
- Before initiating treatment with lithium the following are considerations:
 - complete blood count
 - electrolyte determinations
 - thyroid function tests
 - renal panel
 - EKG
- Blood lithium level should be obtained 12 hours after the last dose
- Drugs that increase lithium level include:
 - ACE inhibitors
 - alprazolam
 - antipsychotics
 - Prozac
 - NSAID
 - thiazide diuretics such as furosemide, hydrochlorothiazide, ethacrynic, and bumetanide (Bumex)
 - spironolactone, amiloride, triamterene
 - Indocin (indomethacin)
 - metronidazole (Flagyl)
- Drugs that decrease lithium levels include:
 - aminophylline
 - caffeine
 - carbonic anhydrase inhibitors such as acetazolamine
 - laxatives
 - osmotic diuretics such as mannitol and urea
 - theobromine diuretics
 - theophylline
- Drugs and procedures that increase adverse reactions while on lithium include:
 - carbamazepine/Tegretol (antithyroid effects)
 - chlorpromazine/Thorazine (EPS, confusion)
 - clozapine/Clozaril (neurotoxicity)
 - diltiazem/Cardizem (neurotoxicity)
 - ECT
 - fluoxetine/Prozac (lithium toxicity)
 - haloperidol/Haldol (neurotoxicity)
 - hydroxyzine/Vistaril (CV toxicity)
 - iodine (antithyroid effects)

- methyl dopa/Aldomet (hypertension)
- metronidazole/Flagyl (lithium toxicity)
- neuroleptics (EPS, neurotoxicity, sleepiness)
- The antimanic effect of both lithium and valproate is 1 to 2 weeks
- Lithium exhibits a specific antisuicide effect; it reduces suicide seven-fold
- Relapse rate in bipolar disorder is 79% with placebo and 37% with lithium
- Desired maintenance lithium plasma level is 0.8 to 1.0 mEq/L
- The tremor side effect from lithium is often treated with beta blockers
- People on lithium maintenance are sometimes monitored for:
 - blood levels every 3 months, renal function with BUN and Cr every 6 months
 - thyroid function with TSH and free T4 every 6 months, and an annual EKG for men over 40 and women over 50 years of age
- Prolonged lithium plasma levels above 2.0 mEq/L can cause CNS damage, renal collapse, coma, and death; signs of lithium intoxication include confusion, ataxia, and tremor
- Common side effects of lithium are: GI (nausea, vomiting, diarrhea), tremor, polydipsia, polyphasia, and polyuria; beta blockers are used to treat the tremor; diuretics for the polydipsia/polyuria (paradoxical effect; diuretics can also increase plasma lithium); potassium supplementation may be needed; GI problems can be treated by switching to slow release preparations; rare bradycardia from slowing of the sinus node can be treated by stopping the lithium or by a pacemaker
- Other side effects of lithium include: rash, fatigue, headache, memory impairment, increased weight, ataxia, constipation, CV, DM, edema, increased WBC, EPS, increased calcium, hypermagnesemia, hyperparathyroidism, hypothyroidism, hyperthyroidism, metallic taste, nystagmus, OBS, osteopenia, osteoporosis, adenomas, blurred vision, ringing in ears, vertigo
- Lithium is associated with an increased risk of Ebstein's anomaly; Ebstein anomaly is a defect of the tricuspid valve of the heart
- A drug that increase absence seizures (rare) if used with lithium is clonazepam (Klonopin)

valproate (Depakote)

- Valproate has several mood stabilizing effects:
 - blocks voltage-sensitive sodium channels
 - influences GABA metabolism
 - influences gene transcription through activity on histone deacetylase
 - influences phosphoinositol
 - reduces PKC (protein kinase C) activity
- Valproate is available in two forms:
 - valproic acid (Depakene)
 - divalproex sodium which is the best tolerated of the two (Depakote, Depakote ER) or sodium valproate (Depakote syrup)
- Valproate is preferred to lithium in certain conditions:

- psychosis
 - rapid cycling
- Laboratory value considerations include: baseline liver values and CBC; these are sometimes repeated every 1 to 4 weeks for the first six months and then sometimes every three to six months
- The starting dose of divalproex has sometimes been as fast as 750 mg/day
- The desired blood level of divalproex is 50 to 125 ng/ml
- The slow-release of divalproex reduces GI side effects
- Valproate increases lamotrigine plasma levels
- Various side effects of valproate include: GI (the most common side effect), hair loss, tremor, sedation, weight gain, pancreatitis, hematological dysfunction such as macrocytic anemia, ataxia, bone marrow suppression, CNS, rash, breast enlargement, dysarthria, edema, enuresis, eosinophilia, hallucinations, galactorrhea, headache, liver damage (more in children), decreased sodium, amenorrhea, lymphocytosis, leucopenia (with Depakote ↓ WBC is more likely; with lithium ↑ WBC is more likely), nystagmus, swelling of parotid gland, porphyria, photosensitivity, itching, thrombocytopenia, Stevens-Johnson rash, SIADH, low platelets, thyroid abnormalities, and polycystic ovary syndrome
- GI side effects are common with divalproex sodium but is less so with the enteric-coated form; H2 antagonist (Pepcid) decreases the GI side effects
- Valproate is metabolized by P450 2D6; it tends to inhibit the degradation of other drugs metabolized in the liver; it is highly protein bound and thus, coadministration with other highly protein bound drugs such as aspirin will increase valproate blood levels
- Valproate increases plasma concentrations of carbamazepine, lamotrigine, and phenobarbital
- Drugs that decrease valproate plasma levels include: carbamazepine (Tegretol), phenobarbital, rifampin, and phenytoin (Dilantin)
- A drug that increases valproate plasma levels is aspirin
- Valproate increases the plasma levels of several other drugs including:
 - diazepam (Valium)
 - barbiturates
 - ethosuximide (Zarontin)
 - phenytoin (Dilantin)
 - phenobarbital
 - TCA
 - tolbutamide (Orinase), for diabetes mellitus
 - zidovudine (Retrovir) for HIV
- Valproate causes an increased for HIV risk of bleeding with some drugs: ASA, NSAID, and sulfinopyrazone (Antazone)
- Valproate can cause CNS depression with several drugs: alcohol, clozapine, neuroleptics, loxapine (Loxitane), maprotiline (Ludimil), MAOI, phenothiazines, pimoxime (Orap), TCAs, and even bupropion (Wellbutrin)

- ASA ↑ Depakote but not lithium; NSAIDs (except ASA and sulindae/Clinoril do ↑ lithium and also ↑ risk of bleeding with valproate); NSAIDs ↑ both Depakote and lithium

carbamazepine (Tegretol)

- Carbamazepine has several mood stabilizing effects:
 - blocks sodium channels
 - increases acetylcholine in the striatum
 - decreases dopamine and GABA turnover
 - decreases norepinephrine release
 - reduces phosphoinositol signaling
 - reduces adenylate cyclase and guanylate cyclase
- Autoinduction of carbamazepine may delay steady state for 1 month
- Plasma protein binding of carbamazepine is 80%
- Carbamazepine compared to dipvalproate has less risk of certain side effects:
 - weight gain
 - tremor
 - hair loss
 - CV
 - GI
 - fetal toxicities such as neural tube defects
- Carbamazepine has greater risk than divalproate of other side effects:
 - dizziness
 - ataxia
 - double vision
 - agranulocytosis
 - induction of hepatic enzymes
 - vertigo
- Carbamazepine has been started at as much as 200 to 400 mg/day in 3 to 4 divided doses and sometimes increased 800 to 1000 mg/day by the end of the first week
- The desired blood level of carbamazepine is 4 to 15 ng/ml
- Carbamazepine decreases lamotrigine plasma levels
- 60% of patients on carbamazepine respond compared to 22% on placebo
- Carbamazepine is started by some at 100 mg/day and increased by 100 mg every four days to a therapeutic range of 4 to 15 ng/mL; the usual base is 400 to 1800 mg/day; because of enzyme induction the dose may need to be eventually increased
- Carbamazepine treatment has at times included frequent blood monitoring the first few months
- The antidiuretic hormone-like effect of carbamazepine may counter the polyuria effect of lithium when they are used concurrently. Thus,
 - carbamazepine - ↓ urine quantity
 - lithium - ↑ urine quantity
- Drugs that increase plasma levels of carbamazepine include:
 - cimetidine (Tagamet)

- diltiazem (Cardizem)
- erythromycin
- fluoxetine (Prozac)
- fluvoxamine (Luvox)
- isoniazid (INH), a TB drug
- propoxyphene (Darvon)
- valproate (Depakote)
- verapamil (Calan)
- Drugs that decrease plasma levels of carbamazepine include:
 - phenobarbital
 - primidone (Mysoline)
 - phenytoin (Dilantin)
- Drugs that are decreased by carbamazepine are many including:
 - neuroleptics
 - most benzodiazepines
 - steroids
 - birth control pills
 - thyroid
 - TCAs
- Carbamazepine (Tegretol) plus lithium can cause neurotoxicity
- Carbamazepine ER (Equetro) is approved for bipolar mania and bipolar mixed

lamotrigine (Lamictal)

- Lamotrigine has several mood stabilizing effects
 - blocks sodium channels
 - inhibits the release of glutamate and aspartate
 - blocks calcium channels
 - inhibits serotonin reuptake
- Lamotrigine is metabolized by glucuronic acid conjugation
- Lamotrigine has protein binding of 55%
- Side effects of lamotrigine include: skin rash (10%; 1 in 1000 proceed to Stevens-Johnson syndrome), dizziness, ataxia, sleepiness, headache, blurred vision, double vision, and GI (nausea, vomiting)
- Drugs that decrease lamotrigine include:
 - carbamazepine (Tegretol)
 - oxcarbazepine (Trileptal)
 - phenobarbital
 - phenytoin (Dilantin)
- Valproate (Depakote) increases lamotrigine levels

neuroleptics

- The atypical neuroleptics are approved as mood stabilizers in various stages of bipolar disorders: Risperdal (risperidone), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), and Abilify (aripiprazole).
- Benefits of clozapine/Clozaril include: less EPS, less TD
- Dangers of clozapine include: increasing lipids, agranulocytosis, diabetes mellitus, seizures, cardiorespiratory complications, weight gain

- Benefits of olanzapine include: less EPS, less hyperprolactinemia
- Dangers of olanzapine include: weight gain, constipation, akathisia, dry mouth, diabetes mellitus, orthostatic hypotension, tremor, tachycardia, sedation (most common side effect), seizures (.9%), and liver damage
- Treatments for weight gain from olanzapine include: topiramate and H2 blockers
- Olanzapine and risperidone usually do not interact with lithium
- Olanzapine does not interact with valproate
- Antipsychotics tend to carry a low risk of fetal abnormalities; higher potency neuroleptics are often safer
- 5HT2A antagonism decreases glutamate and this decreases mania

oxcarbazepine (Trileptal)

- Oxcarbazepine has only 40% protein binding and therefore less drug-drug interactions. Incidentally, carbamazepine has 80% protein binding; lamotrigene has 55%; lithium has low protein binding.

topiramate (Topamax)

- Topamax might be helpful in comorbid bipolar disorders: obesity, obesity with binge eating, bulimia, alcohol dependency, and migraine

zonisamide (Zonegran)

- The jury is still out on Zonegran in bipolar disorder; it is helpful in comorbid obesity

levetiracetam (Keppra)

- Levetiracetam (Keppra) binds to SV2A protein on synaptic vesicles and thus alters neurotransmission by altering neurotransmitter release and producing anticonvulsant and possible mood stabilizing actions
- Benzodiazepines have often been used as adjunctive treatments in mania
- NMDA antagonists (memantine or Namenda, lamotrigene, and riluzole) that decrease glutamate have been tried in bipolar mood disorders
- Amantadine (Symmetrel) has been suggested for bipolar disorder. It decreases glutamate but increases dopamine; it also has effects on the sigma receptor.
- Ketamine blocks NMDA receptors inside the calcium channel and thereby decreases glutamate. It also has effects at sigma receptors. It has shown a rapid antidepressant effect in testing in bipolar patients.
- Gabapentin (Neurontin) and pregabalin (Lyrica) have been used as adjunctive treatments in bipolar patients with anxiety, pain, or seizures. They work on N and P/Q VSCC (voltage sensitive calcium channels). They are alpha 2 delta ligands.
- The natural products of omega-3 fatty acids that inhibits phosphokinase C (PKC), Inositol with effects on secondary messengers and L-methylfolate have been tried in bipolar disorder.
- Zonisamide (Zonogran) and topiramate (Topamax) have been used as adjuncts in bipolar disorder with obesity, alcohol abuse, and other substance abuse

- Bifeprunox (dopamine partial agonist or DPA, 5HT1 partial agonist, no 5HT2A); iloperidone (a serotonin dopamine antagonist or SDA), and asenapine (a SDA)—all new antipsychotics will be examined for mood stabilizing effects.
 - Eslicarbazepine, a metabolite of oxcarbazepine and a new anticonvulsant will be examined for mood stabilizing effects.
 - Dextromethorphan with sigma 1 effects will be examined for mood stabilizing effects.
- **mood stabilizers: year approved**

Acute Mania	Maintenance	Depression
lithium – 1970	lithium – 1974	
chlorpromazine – 1973		
divalproax – 1994		
olanzapine – 2000		
risperidone – 2003	lamotrigine – 2003	olanzapine/fluoxetine – 2003
quetiapine – 2004	olanzapine – 2004	
ziprasidone – 2004		
aripiprazole – 2004	aripiprazole - 2005	
carbamazepine – 2004		quetiapine – 2006

- **Conclusion**
- **Bible verses**
 - Nahum 1:7 – The Lord is good, a strong hold in the day of trouble; and he knoweth them that trust in him.
 - I Peter 5:7 – Casting all your care upon him; for he careth for you.