Oregon ECHO Network

PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

OHSU Adult Psych ECHO
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Objectives

By the end of the session, participants will be able to:

- Identify preferred treatment regimens for bipolar disorder in the acute manic phase, acute depressive phase, and maintenance phase
- Identify important medication-specific monitoring parameters and adverse effects when treating bipolar disorder
- Identify appropriate dosing for medications used to treat bipolar disorder, including considerations for drug-drug and drug-food interactions

APA 2002/2005 Guidelines

- Free to public: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- 2002 Practice Guideline, 2005 Guideline Watch, Quick Reference Guide

- Note: Also sometimes used: NICE guidelines
  - National Institute for Health and Care Excellence
  - Can be found at: https://www.nice.org.uk/guidance
  - Not reviewed here except where noted

APA 2002/2005 Guidelines

Abbreviation	Drug
Li	Lithium
VPA	Valproate/Valproic acid/Divalproex
LMT	Lamotrigine
SGA	Second Generation Antipsychotic
CBZ	Carbamazepine
OXC	Oxcarbazepine
SSRI	Selective Serotonin Reuptake Inhibitor
ECT	Electroconvulsive Therapy
MAOI	Monoamine Oxidase Inhibitor

Episode Type	Treatment Goals by Type	Drug Classes Utilized (per APA Guidelines)
Acute Manic Episode	•Control of acute symptoms to allow a return to usual levels of psychosocial function •Rapid control of agitation, aggression, impulsivity if present •Stabilization of symptoms •Remission	Mood stabilizer/antimanic •Lithium Antiepileptics •Divalproex/Valproate/Valproic Acid •Carbamazepine•Oxcarbazapine Antipsychotics •Haloperidol•SGAs•Clozapine
Acute Depressive Episode	•Remission and return to usual levels of psychosocial functioning •Avoid precipitating manic/hypomanic episode	Mood stabilizer/antimanic •Lithium Antiepileptics •Lamotrigine Antidepressants •SSRIs•SNRIs•Bupropion Antipsychotics •SGAs
Maintenance Treatment	•Reduce residual symptoms •Prevent relapse & recurrence •Improve overall functioning	Mood stabilizer/antimanic •Lithium Antiepileptics •Divalproex/Valproate/Valproic Acid •Carbamazepine•Oxcarbazapine Antipsychotics •Haloperidol•SGAs•Clozapine

	Acute Manic	Acute Depressive	Maintenance
1st Line	Severe Manic/Mixed: - Li + SGA , or - VPA + SGA *Alternative to Li or VPA: CBZ or OXC *VPA preferred in mixed Less severe manic: - Li, VPA, or SGA monotherapy	Severe: - Li + SSRI Less severe: - Li or LMT *With psychotic features: add SGA (ECT is alternative) *Consider ECT if suicidal/violent/severe + pregnant	- Most recent episode hypomania, Mania: Li, or VPA or potentially LMT (if not with frequent/severe mania) - Most recent episode depression: LMT or LMT + antimanic agent (frequent/severe mania) *SGA should be stopped except for persistent psychotic sx or recurrence prophylaxis
2nd Line	- Add another first line medication (Li, VPA, SGA), or - Add CBZ or OXC, or - Switch SGA if already initiated	- Add another med: LMT, different SSRI (guidelines indicate paroxetine) *Alternatives to LMT/SSRI: venlafaxine, bupropion (guidelines also suggest MAOI) *With severe/treatment-resistant/psychotic/catatonic features: consider ECT	- Most-recent episode hypomania, mania: aripiprazole - Most recent episode depression: lithium
3rd Line	Combination therapy: - Add/switch SGA/clozapine - Add ECT	N/A	- Most-recent episode hypomania, mania: CBZ, clozapine - Most recent episode depression: antimanic + antidepressant, olanzapine + fluoxetine

*Short-term benzodiazepine adjunct appropriate upon initiation of tx in severe acute manic/mixed episode

Mood Stabilizer/Antimanic: Lithium

- Best agent for improvement of suicidality
- Preferred over LMT in maintenance when manic/hypomanic most recent
- ADEs occurring at therapeutic range (up to 75%)
  - GI problems, polyuria, polydipsia, weight gain, fluid retention, cognitive problems, fine tremor, sedation, impaired coordination, hypothyroidism, benign leukocytosis, acne, psoriasis, dermatitis, alopecia
    - Often managed by lowering dose or changing dosing schedule
- Discontinuation
  - Taper if possible, even if other medication is started
    - 2014 NICE guidelines: at least 4 weeks, preferably up to 3 months

Mood Stabilizer/Antimanic: Lithium

- Dosing per APA guidelines:
  - Initial treatment: 300 mg TID or less
  - Maintenance treatment: typically 900-1800 mg/day
    - Dose range: 900-2400 mg/day (two-four divided doses)
    - Once daily dosing up to 1800 mg/day
- Targeted serum concentrations: 0.6-1.2 mEq/L (trough levels – take just before next dose [8-12 hours after previous dose], ideally before AM dose)
  - Acute mania 0.5 to 1.2 mEq/L
  - Maintenance: 0.6 to 1 mEq/L
  - Toxic at > 1.5 mEq/L
  - Emergency at ≥ 2.5 mEq/L, even if asymptomatic
- Serum levels should follow strict monitoring schedule
  - Check ~ 5 days after initiation/dose change (steady-state)
  - Check more often (twice weekly) as serum levels approach 1.0 mEq/L
  - Check every 1-3 months while stable, or if clinical status changes
  - Note: 300 mg dose change typically leads to approx. 0.3 mEq/L change

Mood Stabilizer/Antimanic: Lithium

- General Monitoring
  - Baseline: Weight, CBC with differential, Electrolytes (Na^+, K^+), Renal function: BUN, SCr, Urine specific gravity, Thyroid function (TSH, T4), Pregnancy test (Category D), ECG: patients > 40 y.o. or those with h/o of cardiac problems
  - Followup: Weight, Lithium level until stable then q6 months, BUN, creatinine, electrolytes: q2-3 months for 6 months then q6-12 months, TSH and T4: once or twice during 6th month then q6-12 months, ECG: annually in patients > 40 y.o. or those with h/o of cardiac problems

Mood Stabilizer/Antimanic: Lithium

- Thyroid function
  - Thyroid fx 1-2 times first 6 months
  - Check every 6-12 months for several years if stable
  - Check if clinical status changes
  - Discontinuation of lithium is not necessary if hypothyroidism occurs, but need to treat hypothyroidism
- Renal function
  - Renal fx every 2-3 months first 6 months
  - Check every 6-12 months for several years if stable
  - Check if clinical status changes
  - Morphologic changes in kidneys leading to diminished renal concentration can occur
    - May not present until 10 years after initiation (10-20%)
    - Changes not typically associated with renal failure, but if insufficiency occurs, usually reversible if lithium stopped

Mood Stabilizer/Antimanic: Lithium

- Drug-food interactions
  - Food has no effect on absorption
  - Dehydration can cause toxicity relatively easily
  - Salt restriction causes increased levels
  - Caffeine causes decreased levels
- Drug-drug interactions
  - Generally any drug that affects kidney fx, water balance, or salt balance can lead to change in levels
    - Increases lithium level: thiazide diuretics, NSAIDS (excluding ASA), ACE inhibitors, tetracyclines, metronidazole
    - Decreases lithium level: potassium-sparing diuretics, theophylline
    - May increase or decrease level: loop diuretics, calcium channel blockers

Antiepileptics

- Manic/hypomanic episode
  - Divalproex/valproate/valproic acid:
    - 1st line in mania as well as maintenance with manic/hypomanic episode most recent
    - Best for rapid cycling
  - Carbamazepine: 1st line alternative in mania/hypomania, 3rd line as maintenance with hypomanic/manic episode most recent
  - Oxcarbazapine
- Depressive episode (and sometimes hypomania if rapid cycling)
  - Lamotrigine: shown to increase time to next depressive episode

Antiepileptics – VPA

- VPA = Divalproex, valproate, valproic acid
- Dosing
  - Acute mania, hospitalized: initial dosage 20-30 mg/kg/day
    - Titrate to goal serum level of 50-125 µg/mL
  - Outpatients, elderly patients, or patients with hypomania or euthymia: initial dosage 250 mg TID
    - Titrate to response/side effects by 250-500 mg/day every few days
      - $t_{1/2}$ = 9-19 hours in adults
    - Typical effective serum concentration 25 µg/mL
      - Max adult dose 60 mg/kg per day
      - Once stable, may simplify regimen if possible (QDay-BID dosing)
- Bioavailability of divalproex ER ~15% less than IR formulations
- Food delays absorption, but does not reduce extent of absorption
  - Can take with food in cases of GI upset

VPA Drug-Drug Interactions

- Notable interactions (not comprehensive list)
  - Highly protein-bound (80-90%); displaces other highly protein-bound drugs from binding sites
  - Hormonal contraception (estrogen)
    - Decreased serum VPA (monitor closely)
  - Lorazepam
    - VPA may increase lorazepam concentrations
  - Carbapenems
    - Significantly decreased serum VPA
  - Carbamazepine
    - VPA may increase active CBZ metabolites; parent compounds may be increased, decreased, or unchanged. CBZ may decrease serum VPA
  - Oxcarbazepine
    - VPA may decrease serum OXC

Antiepileptics – Lamotrigine

- Typical lamotrigine titration: 25 mg/day for 2 weeks, then 50 mg/day for 2 weeks, then 50 mg added weekly as clinically indicated up to 200 mg/day
  - Titration over 6 weeks to avoid Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
    - If rash occurs, must stop immediately, no rechallenge
- Initial dosing depends on what other drugs interact
  - Interactions cause $t_{1/2}$ to vary from 8-89 hours depending on drug
- If skip > 5 half-lives, need to restart titration
- Food does not affect absorption

LMT Drug-Drug Interactions

- Notable interactions (not comprehensive list)
  - Hormonal contraception (estrogen)
    - Decreased serum LMT (reduction in dose may be needed during pill-free week if not taking continuously)
  - Carbamazepine
    - LMT can enhance CBZ ADE/toxicity; CBZ can increase LMT metabolism
  - Acetaminophen
    - Can decrease LMT serum concentration
  - CNS depressants
    - Increased depressant effects

Initiating VPA + LMT

- Major interaction!!!
  - LMT serum levels can double
  - Need to titrate LMT slower than usual/lower dosing
    - Typical lamotrigine titration: 25 mg/day for 2 weeks, then 50 mg/day for 2 weeks, then 50 mg added weekly as clinically indicated up to 200 mg/day.
    - With VPA, dosing is half of typical dose (i.e. start at 12.5 mg/day for 2 weeks, then titrate to 25 mg/day for 2 weeks, etc., max 100 mg/day)
  - Monitor closely for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (signs of rash)

Second Generation Antipsychotics

- Used in acute manic/mixed episode, esp. with psychosis
- Used in acute depressive episode ONLY if psychotic features present
- Used in maintenance if persistent psychotic features or to prevent recurrence
  - Can be considered for maintenance, but less evidence than other agents
- Preferred SGAs per guidelines:
  - Olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole
    - Olanzapine and risperidone: most evidence for mixed/mania
- Be mindful of effect of food on absorption of different SGAs

Second Generation Antipsychotics

TABLE 1. **Dosing and Relative Side Effects of Second-Generation Antipsychotic Agents for the Treatment of Acute Mania or Mixed Episodes**

Medication	Initial Dosing[a]	Typical Dose Range	Weight Gain, Glucose and Lipid Abnormalities	QTc Prolongation	Sedation and Hypotension	Anticholinergic Effects
Aripiprazole	30	10–30	0	0	0/+	0
Risperidone	3	2–8	++	+	+	0
Olanzapine	10–15	10–30	+++	0	+	++
Quetiapine	100	300–800	++	0	++	0
Ziprasidone	80	120–200	0	++	0	0

0 = No risk or rarely causes side effects at therapeutic dose. + = Mild or occasionally causes side effects at therapeutic dose.
++ = Sometimes causes side effects at therapeutic dose. +++ = Frequently causes side effects at therapeutic dose.

[a]Lower starting doses may be indicated for outpatients, elderly patients, or patients taking other medications with potential drug-drug interactions.

Second Generation Antipsychotics

(From 2016 slide deck developed by Dr. Ann Wheeler)

Atypical Antipsychotic	Approved FDA Bipolar Indication
Saphris (asenapine)	Acute treatment of manic or mixed episodes associated with Bipolar I Disorder; >9 years
Latuda (lurasidone)	Depressive episode associated with Bipolar I Disorder (Bipolar Depression); Adults
Zyprexa (olanzapine)	Bipolar I Disorder (Manic or Mixed Episodes (mono or adjunctive therapy); >13 years Depressive episodes associated with BD I (with fluoxetine)
Risperdal (risperidone)	Bipolar mania; >12 years
Seroquel (quetiapine) Seroquel XR	Bipolar mania; >9 years Bipolar disorder, depressive episodes Maintenance tx of BD I as adjunct to Li or VPA
Geodon (ziprasidone)	Bipolar I Disorder (acute mixed or manic and maintenance as adjunct to Li or VPA); Adults
Abilify (aripiprazole)	Bipolar I Disorder (acute or maintenance); >10 years Agitation associated with bipolar mania; Adults

Selected adverse effects of antipsychotic medications for schizophrenia

	Weight gain/diabetes mellitus	Hyper-cholesterolemia	EPS/TD	Prolactin elevation	Sedation	Anticholinergic side effects	Orthostatic hypotension	QTc prolongation
First generation agents								
Chlorpromazine	+++	+++	+	++	+++	+++	+++	+
Fluphenazine	+	+	+++	+++	+	–/+	–	ND
Haloperidol	+	+	+++	+++	++	–/+	–	+
Loxapine	++	ND	++	++	++	+	+	+
Perphenazine	++	ND	++	++	++	+	–	ND
Pimozide	+	ND	+++	++	+	+	+	++
Thioridazine*	++	ND	+	+++	+++	++++	++++	+++
Thiothixene	++	ND	+++	++	+	+	+	+
Trifluoperazine	++	ND	+++	++	+	+	+	ND
Second generation agents								
Aripiprazole	+	–	+	–	+	–	–	–/+
Asenapine	++	–	++	++	++	–	+	+
Brexpiprazole¶	+	+	+	–/+	+	–/+	–/+	–/+
Cariprazine¶	+	–/+	++	–/+	+	–/+	–/+	–/+
Clozapine[Δ]	++++	++++	–/+	–/+	+++	+++	+++	+
Iloperidone	++	++	–/+	–/+	+	+	+++	++
Lurasidone	–/+	–/+	++	–/+	++	–	+	–/+
Olanzapine	++++	++++	+	+	++	++	+	+
Paliperidone	+++	+	+++	+++	+	–	++	+
Pimavanserin	+	-	-/+	-	+	+	++	+
Quetiapine	+++	+++	–/+	–/+	++	++	++	+
Risperidone	+++	+	+++	+++	+	+	+	+
Ziprasidone	–/+	–/+	+	+	+	–	+	++

Adverse effects may be dose dependent.

Chart from UpToDate

Antidepressant Medications

- Review previous lecture on medications for treatment of depression
- Classes: SSRIs (typically fluoxetine, but paroxetine, citalopram may be an option), SNRI (venlafaxine), DNRI (bupropion)
- Severe depressive episode: 1st line in combination with lithium
- Maintenance with depressive episode most recent: 3rd line in combination with lithium or olanzapine
- NOT used in mania/hypomania
- **NEVER USE AS MONOTHERAPY!!!!!!!**

Special Consideration: Rapid Cycling

- If on antidepressant, may be contributing and should be tapered off
  - Unclear if it is antidepressant use vs. nature of rapid cycling being predominantly depressive episodes
- Can be precipitated by hypothyroidism
- Initial treatment should include lithium or valproate
  - Some studies show divalproex more effective than lithium, but had many confounders
  - Some studies show rapid cycling relatively unresponsive to lithium or carbamazepine, as these act mostly on manic phase
  - Divalproex + lithium may lead to good outcomes
  - Lamotrigine is alternative to first line – not effective for severe mania, but significant improvement in hypomania and depression w/ rapid cycling
- Many need combination therapy
  - Limited data, but best combo may be divalproex + lamotrigine

Special Consideration: Breakthrough Mania/Mixed Episode

- Maximize dose of current regimen
  - Ensure therapeutic serum levels; increase dose if possible (even if therapeutic already)
- Consider antipsychotic
- If severe or agitated, consider benzodiazepine

Special Consideration: Pregnancy

- Patients should be counseled on effective birth control
  - Lithium, valproate, or carbamazepine cause birth defects
    - If these are continued, screening for neural tube defects should be performed
    - Lithium levels can fluctuate during pregnancy, and rapidly during delivery
      - Lithium should not be stopped in this case, but dose should be lowered and care taken to keep patient hydrated
  - Inadequate information for antidepressants
  - High-potency antipsychotics are an option with minimal risk
    - Risk with SGAs unclear – avoid
  - Despite risks, treatment during pregnancy is generally still recommended
    - No data on effects of BD on fetus itself, but can assume possible deleterious effect due to what is known about effects of high stress levels in pregnancy
  - Treatment during postpartum period essential
  - Recommend bottle feeding due to high levels of drug secreted in breastmilk

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Questions?