Overview of The Treatment of Bipolar Mood Disorder

Nurse Practitioners of Idaho
Lifetime prevalence of Bipolar Disorder in the US is 4.5%
- 1% Bipolar I,
- 1.1% Bipolar II,
- 2.4% Bipolar NOS

Rate of completed suicide is 5% among those never hospitalized

Rate of completed suicide is 25% early in the course of the illness

The NIMH Collaborative Depression Study followed patients for 12 years: patients were symptomatic nearly 50% of the time (depressed 1/3 of the time)

Objectives for Today

- Review diagnostic essentials
- Review of EBT algorithms and guidelines
- A few updates from the literature
- Dosing and safety monitoring for selected medications
Diagnostic Essentials

- Screening question:

  “Have there been times, lasting at least a few days, when you felt the opposite of depressed, when you were very cheerful or happy and this felt different from your normal self?”

- If yes, ask:

  - “Did you feel this way all day or most of the day?

  - Did these times ever last at least a week or result in your being hospitalized?

  - Did these periods ever cause you significant trouble with your friends or family, at work, or in another setting?”

The Pocket Guide to the DSM-5 Diagnostic Exam, Abraham Nussbaum, M.D. 2013
Bipolar I Disorder

Diagnoses requires history of a Manic Episode:

A. A distinct period of abnormally elevated, expansive or irritable mood with persistently increased goal-directed activity or energy lasting at least 1 week and present most of the day, nearly every day (or any duration requiring hospitalization).

Desk Reference to the Diagnostic Criteria From DSM-5 2013
B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

- Inflated self-esteem or grandiosity
- Decreased need for sleep (3 hours or less)
- More talkative than usual or pressure to keep talking
- Distractibility
- Increase in goal-directed activity (socially, at work, or sexually) or psychomotor agitation
- Excessive involvement in activities that have a high potential for painful consequences
C. The Mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criterion A-D above constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of Bipolar I Disorder.
Bipolar II Disorder diagnoses requires current or past hypomanic episode and current or past major depressive episode

Hypomanic episode criteria are similar to those for a Manic episode except for duration (4 consecutive days), and for the severity of symptoms.

While they must be observable to others as an “unequivocal” change in mood or behavior, it is not necessary that they result in severe social or occupational impairment.

Desk Reference to the Diagnostic Criteria From DSM-5 2013
Diagnostic Essentials

- Comprehensive psychiatric assessment including:
  - Longitudinal mood history with detailed symptoms, any past treatment and response
  - Detailed social history (relationships, employment, legal, substance abuse)
- Consideration of any other medical or cause for symptoms
- Collateral information if available
- Careful attention to diagnostic criteria
Diagnostic Essentials

- Are there people with cyclic mood disorders who don’t quite meet these criteria?
- How do so many people end up with this diagnoses?
- What are differential diagnoses for BMD?
  - MDD
  - Cyclothymic disorder
  - Schizoaffective disorder
  - Anxiety disorders
  - ADHD
  - Personality disorders
  - Other bipolar disorders
  - Substance-induced bipolar disorder
  - Bipolar disorder due to another medical condition
Treatment Considerations

- **Patient Profile:**
  - severity of symptoms and any physical health concerns
  - any factors that would affect the way the patient’s ability to take medications

- Treatment algorithms
- EBT guidelines
- Clinical experience
Texas Implementation of Medication Algorithms (TIMA)

- TMAP Project (Texas Medication Algorithm Project)
  - Started in 1995 for Schizophrenia, Bipolar I Disorder and Major Depressive Disorder to incorporate best practices and EBT into Texas Mental Health System.
  - Guidelines were last updated in 2007.
Texas Implementation of Medication Algorithms (TIMA)

- **TIMA – 2007: Mania/Mixed:**
  - Euphoric (Classic) Mania/ For Mixed (No Li or QTP)
  - **Stage 1:** Monotherapy (Benzos concurrently, PRN)
    - LI, VPA, ARP, QTP, RIS, ZIP
    - OLZ or CBZ as less preferred alternatives
  - **Stage 2:** Two-Drug Approach
    - LI or VPA + SGA
    - NOT 2 SGAs
    - NOT Abilify or Clozaril
  - **Stage 3:** Switch to different 2-drug combo
  - **Stage 4:** ECT or add Clozaril or add SGA to Li + (VPA, CBZ or OXC)
Texas Implementation of Medication Algorithms (TIMA)

- TIMA – 2007 Bipolar Depression
  - **Stage 1:**
    - If taking Li, increase to 0.8 mEq/L
    - If taking other antimanic, continue
    - If taking no antimanic w/HX of severe/recent mania: antimanic + LTG
    - If no HX of severe/recent mania: LTG as monotherapy
  - **Stage 2:**
    - **Switch to:** QTP monotherapy OR Olanzapine + Fluoxetine (Symbyax) a.k.a. OFC
Texas Implementation of Medication Algorithms (TIMA)

- **Stage 3:**
  - Two-drug combination: (Li, LTG, QTP, or OFC)

- **Stage 4:**
  - (Li, LTG, QTP, OFC, VPA, or CBZ) + (SSRI, Bupropion or Venlafaxine) or ECT

- **Stage 5:**
  - MAOIs, TCAs, Pramipexole (Mirapex: a Dopamine Agonist used in Parkinson’s RX), other SGAs, OXC, other combos, inositol (supplement), stimulants, thyroid, (fish oil/omega-3 FAs)
Psychopharmacology Algorithm Project Harvard South Shore Project

- PAPHSS Algorithms
  - Internet-based, interactive
  - Mobile platform: [www.psychopharm.mobi](http://www.psychopharm.mobi)
Review of Literature for EBT Guidelines

  - Authors reviewed and summarized all major guidelines and treatment algorithms updated after 2005
  - World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the Biological Treatment of Bipolar Disorder: update 2009 on the treatment of Acute Mania
  - RG from 1-5 (grades of recommendation)
Acute Bipolar Mania

- **First Line:**
  - Lithium especially in euphoric mania RG2
  - VPA and Carbamazepine for dysphoric or mixed
  - Abilify effective across subtypes
  - Risperdal best for severe and psychotic mania
  - Geodon effective in mixed and psychotic mania RG2
  - Olanzapine has broad efficacy RG2
  - Quetiapine RG2 (less effective than Haldol)
  - Haldol RG2
  - Asenapine RG2
Number Needed to Treat

- **NNT**
  - Number of patients to yield 1 more good outcome (response)
  - Calculation:
    - \( \frac{100}{(\text{Drug response}\% - \text{placebo response}\%)} = \text{NNT} \)
    - If Drug response is 50% and placebo response is 30% then \( \text{NNT} = \frac{100}{(50-30)} = \frac{100}{20} = 5 \) (lower numbers are better)
# NNT: Acute Bipolar Mania

| 4: | Lithium |
| 4: | Carbamazepine |
| 4: | Risperidone |
| 4: | Haloperidol |
| 5: | Olanzapine |
| 5: | Aripiprazole |
| 6: | Quetiapine & Quetiapine XR |
| 7: | Divalproate & Divalproate ER |
| 7: | Ziprasidone |
| 8: | Asenapine |

Meekile N. Mason, M.D., NPA  17th ANNUAL Psychopharmacology Conference, February 2012
Acute Bipolar Mania

- Second Line:
  - Lithium and/or an AED plus antipsychotic
  - Invega monotherapy
  - Clozapine in refractory mania, both euphoric and dysphoric
  - Clonazepam and Lorazepam as add-ons to relieve anxiety and agitation
  - Topiramate, Lamotrigine, Gabapentin are not recommended
  - Carbamazepine in combination with either Olanzapine or Risperdal not recommended
Other Studies

- In a meta-analysis of RCT comparing one active antimanic drug with another or with placebo, the authors found that overall antipsychotics were significantly more effective than mood stabilizers, with Risperdal, Olanzapine and Haloperidol showing the best efficacy profile in the treatment of acute manic episodes.
  - Cipriani, et. al. 2011.

- Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple treatments meta-analysis.
  - Lancet
Consensus for Treatment of Mania

- Stop Antidepressants
- Start with monotherapy with Lithium, Valproate or an Atypical Antipsychotic
- Short term use of benzodiazepines as adjuncts
- Consensus on what drugs not to use (Lamictal, Trileptal, Gabapentin, Topiramate)
Drug-Induced Mania: Culprits

- Corticosteroids (withdrawal may also precipitate depression)
- Dopamine agonists
- Antidepressants
- Aggravators:
  - Caffeine
  - Theophylline
  - Methamphetamine, cocaine, etc.
Number Needed to Harm

- **NNH**
  - Number of patients to yield 1 more poor outcome (response)
  - Calculation:
    - $\frac{100}{\text{(Drug sedation rate\% - placebo sedation rate\%)}} = \text{NNH}$
    - If Drug response is 50\% and placebo response is 30\% then $\text{NNH} = \frac{100}{(50-30)100-20} = 5$
      - (higher numbers are better)
Acute Bipolar Depression


- Management is complex and guidelines are evolving
- Quetiapine has gained acceptance as 1st line monotherapy across all guidelines
- Other Atypicals, Lithium and VPA still appear in guidelines
- Lamotrigine has become a more controversial option
- Antidepressants are generally discouraged
- 2nd Line: adjunctive Mirtazapine, Effexor, TCAs
Treatment Options for Acute Bipolar Depression

- Olanzapine/Fluoxetine Combination
- Quetiapine
- Lurasidone
NNT for Bipolar Depression

- NNT, Bipolar Depression:
  - 4: Olanzapine/Fluoxetine combination
  - 6: Quetiapine & Quetiapine XR
  - 11: Lamotrigine
  - 12: Olanzapine
  - Unknown for Valproate

*Latuda is recently FDA approved for Bipolar Depression

Meekile N. Mason, M.D., NPA 17th ANNUAL Psychopharmacology Conference, February 2012
Lithium

- First-Line standard of care since early 1970’s
- Efficacy across the spectrum of Bipolar Disorder
- Best evidence for reduction in suicidal ideation
- May be neuroprotective
- Lithium plus Depakote more effective than either alone (Balance Study, UK)
- Lithium alone more effective than Depakote alone (Balance study, UK)
- Use began to decrease in 1990’s with introduction of other options
- Only about 1/3rd of current patients diagnosed with bipolar disorder take lithium
Lithium

- Relevant Pharmacokinetics:
  - Rapid complete absorption with high peaks causing most side effects therefore:
  - Slow absorption with food or SR forms (Food is cheaper)
  - Renal Clearance
  - T ½ = 24-36 hours

- Plasma Concentrations:
  - Steady state in 3-5 days
  - Sample 12 hours after last dose
  - Targets:
    - 0.5 – 1.5 mEq/L based on patient tolerance
    - 0.8 mEq/L or more for depression
    - 1 - 1.5 mEq/L or sometimes higher for acute mania
Lithium Intoxication:

- *Usually*: > 1.5 mEq/L, but highly variable
- Increasing (“Coarsening” tremor)
- Increasing GI effects (NVD)
- Dehydration, electrolyte imbalance, decreased LI elimination
- Ataxia, slurred speech
- Confusion, disorientation
- Seizures, coma, death
Lithium counseling points for patients:

- Take with food to avoid GI discomfort and to slow release
- Tremor will occur with therapeutic doses
- Worsening tremor as early sign of intoxication
- LI may cause weight gain. If patients decrease their sodium or calorie intake while taking Li, the body will hold on to Li and cause toxicity
- Polyuria, polydipsia early in therapy
- A thiazide diuretic will increase LI by 100% so decrease LI dose by 80% to compensate.
Lithium

- AVOID:
  - Sudden changes in diet (reduced calorie intake)
  - Sodium restriction (diuretics)
  - Dehydration
  - OTC NSAIDS; Never use NSAID Motrin with LI as it will increase LI levels (Tylenol OK)
  - Increased/changed intake of caffeine or xanthine products
  - Abrupt discontinuation
  - Bipolar Disorder is NOT a lithium deficiency
  - Lithium is “natural”; it is a salt
Lithium

- **Monitoring:**
  - **Thyroid function:**
    - Li can cause hypothyroidism/elevated TSH, at least transiently,
    - If elevations in TSH persist, check for goiter and give thyroid replacement

- **Parathyroid Function:**
  - Hypercalcemia/Hyperparathyroidism (Rare)

- **Renal Function:**
  - Change in renal function requires dose change
  - Lithium induced renal dysfunction (?)
  - Urine output: Risk of Lithium-induced nephrogenic diabetes insipidus (L.I.N.D.I.)
Lithium

- L.I.N.D.I.
  - Lithium interference with/blockade of ADH (vasopressin) in renal collecting ducts can cause Polyuria (3-6 L/day) and compensatory Polydipsia
  - Risks of dehydration causing Li retention causing Li Intoxication

- Treatment for L.I.N.D.I.:
  - DC Lithium; reversible
  - Other medical treatment as indicated
Other Studies of Interest

The Bipolar Trials Network Lithium Treatment Moderate Dose Use Study (Litmus): A Randomized Comparative Effectiveness Trial of Adjunctive Lithium (Michael E. Thase, M.D. University of Pennsylvania School of Medicine)

Compared strategies of treatment for 6 months:

1. N = 283
2. Lithium plus optimized treatment (TIMA)
3. Optimized treatment without Lithium
4. Moderate dose 600mg/day (levels 0.5-0.6 mEq/L)
5. No serious AE
6. Only significant outcome: 15-20% reduction in use of SGAs
Valproate (VPA)

- **VPA Dosing:**
  - Reasonable Target Maintenance Dose = 20mg/kg/day (1500-2000mg/day)
  - Loading dose – 20mg/kg on day 1, in 2-3 divided doses, WITH FOOD
  - Depakote/Depakote ER: DO NOT CRUSH OR SPLIT: MAY need increased doses: Depakote ER dose = 120% of VPA or Depakote
  - Depakote Sprinkles can be opened and mixed with food
Valproate (VPA)

- **VPA Dosage Forms:**
  - Valproic Acid (Depakene): rapidly and completely absorbed; $\frac{1}{2}$ life = 12 hours; generic and inexpensive
  - Depakote tablets: Enteric-coated; slightly delayed but complete absorption; more tolerable (?); generics available
  - Divalproex: Depakote ER and Depakote Sprinkles: prolonged absorption; effectively sustained release; Depakote ER bioavailability is 80% of other forms; most expensive
Valproate (VPA)

- **VPA Blood Levels:**
  - Reasonable relationship between pt. response and plasma concentration of 50-125 mcg/ml (Trough)
  - Less relationship between elevated plasma concentrations and likelihood of side effects or toxicity
  - Tough to get true, reproducible, trough plasma concentrations for Depakote or Depakote ER
  - Approximately 90% of VPA is bound to Albumin: Total (bound + unbound) is routinely measured by lab
  - Patients with Low Albumin have increases free fraction and at any given Total level, unbound level is higher; better response at lower levels.
  - Treat the patient not the blood level, target reasonable doses; “low” plasma concentrations aren’t necessarily low in patients with decreased albumin;
Valproate (VPA)

- **VPA Common Side Effects**
  - **GI**: Nausea, heartburn, diarrhea (give with food; switch to Depakote)
  - **Sedation**: Usually transient
  - **Weight Gain**: Common, can be dramatic
  - **Tremor**: Intentional tremor similar to Lithium; Rx with Propanolol
  - **Decreased Platelets**: (reversible with dose reduction)
  - **Thrombocytopenia**
  - **Hair loss**: Usually temporary
  - **Elevated liver enzymes (ALT/AST)**: Early in TX, temporary dose reduction, time
  - **Hepatotoxicity**: Significant elevation in LFTs with abdominal pain, vomiting, jaundice, coagulation deficiencies
  - **Known Teratogen**: Neural Tube defects (Hi dose Folate – 4 mg/day)
Valproate (VPA)

- Potent *Inhibitor* of Hepatic Metabolism of other medications (CYP 450)
  - Lamotrigine: Doubles the $\frac{1}{2}$ life with increased risk of Steven-Johnson syndrome (Use 6 week starter kit for Lamictal based on diagnosis)
- TCAs
Valproate (VPA)

- **Inducers** of hepatic metabolism affecting VPA metabolism significantly (requiring increases in dosage and possibly causing increased risk of VPA-related hepatotoxicity):
  - Phenytoin (Dilantin) levels decreased and VPA levels increased
  - Phenobarbital
  - Carbamazepine
  - Ethanol (in sober patients)
Carbamazepine

Carbamazepine = CBZ

- Carbamazepine (Tegretol)
- Extended Release (Tegretol-XR)
- Sustained Release (Carbatrol & Equetro)

CBZ Dosing:

- Average Target Maintenance Dose: Approx. 15 mg/kg/day (800-1200 mg/day)
- Initial dose: 100-200 mg BID
- Increase every 3-7 days
- Give with food to decrease GI side effects
Carbamazepine

- CBZ Blood Levels:
  - Often not as useful as patient response
  - Trough concentrations 4-12 mcg/ml
  - Active Metabolite: CBZ-10,11-epoxide
    - Not measured with “Tegretol levels:
    - Can accumulate & contribute to both therapeutic and adverse effects
- Autoinduction: CBZ-induction of liver enzymes responsible for its own metabolism can result in decrease in plasma concentrations despite constant dosing
Carbamazepine

CBZ: Common Side Effects:

- Sedation
- GI (nausea, heartburn)
- Diplopia
- Gait disturbance
- Leukopenia (20% of patients): Usually mild (3000-4000); not related to agranulocytosis/aplastic anemia
- Hyponatremia: usually asymptomatic but may mimic CBZ intoxication
- Elevated liver enzymes
Carbamazepine

CBZ: Severe Adverse Reactions:

- Hepatotoxicity
  - Rare; idiosyncratic hypersensitivity
  - Elevated AST/ALT with abdominal pain, jaundice, vomiting, coagulation defects

- Agranulocytosis/aplastic anemia
  - Rare; idiosyncratic hypersensitivity
  - Precipitous drop in WBCs and platelets
Carbamazepine

CBZ Skin Rashes:
- Serious rashes are MORE common with CBZ than with properly dosed LTG
- People of Asian ancestry are more likely to carry HLA-B*1502 allele which increases risk
- FDA “strongly recommends” testing Asian patients before starting CBZ TX

CBZ Teratogenicity:
- Known teratogen: facial clefts, neural tube defects, etc.
- Risk increases with VPA co-medication; probably due to accumulation of epoxide metabolites
- Folate Supplementation: Hi Dose – 4 mg/day
Carbamazepine

**CBZ Potent Enzyme Inducer for:**
- Alprazolam & Triazolam
- VPA
- Amlodipine, Felodipine, etc.
- TCAs (ex. Imipramine)
- Hormonal contraceptives
- Protease Inhibitors
- Lamotrigine
- Many others

**Drugs That May Inhibit the Metabolism of CBZ:**
- Erythromycin & Clarithromycin
- Propoxyphene
- Diltiazem
- Ketoconazole & Fluconazole
- VPA
- Prozac
Oxycarbamazapine (Trileptal)

- Analog of Carbamazepine
- NOT metabolized to active epoxide metabolite
- Less potent as enzyme inducer; less interaction with other drugs
- Usually better tolerated than CBZ
- Probably higher likelihood of hyponatremia
- Less risk of Hepatotoxicity & blood dyscrasias
- 25% cross-reactivity (rash) with CBZ
- Plasma concentrations not useful
Lamotrigine

- Primary Psychiatric application: Bipolar Disorder Maintenance
  - Rare precipitation of acute mania
  - Combine with other mood stabilizers when history includes recent and/or severe manic episodes
Lamotrigine

LTG Pharmacokinetics:

- Monotherapy: Half-life = 24 hours
- With Enzyme Inducers (CBZ, etc.): Half-life = 12 hours
- With Enzyme Inhibitors (VPA, etc.): Half-life = 60 hours
- Protein binding- not significant
- Plasma concentrations –not defined relative to therapeutic response
Lamotrigine

Dosing is critical:

- Initiation & titration must be done slowly
- Start: No more than 25 or 50 mg/day
- If patient takes VPA: cut LTG dose by 50% QOD
- Increase dose no more often than every 1-2 weeks
- BID or QD dosing
- “Starter Pack”
Lamotrigine

Common Side Effects:
- Sedation
- Diplopia
- GI Side Effects

Serious Adverse Effects:
- Skin Rash/Hypersensitivity usually early onset (4 - 6 weeks)
- Generalized erythematous, morbilliform rash: mild or progress to Stevens-Johnson and/or Toxic Epidermal Necrolysis
- Risk increase with rapid/large dose increases and/or aggressive titration
- If dosed properly, severe skin rashes are less common than those with CBZ
Lamotrigine

LTG Drug Interactions:

- Inhibition of LTG Metabolism by VPA
- Induction of LTG Metabolism by CBZ, Oral Contraceptives and other classic enzyme inducers

Pharmacodynamic Interactions: sedation & cognitive disturbance when combined with CBZ:

- Additive pharmacologic effects
- Reduce dose of CBZ
- NOT related to CBZ - epoxide metabolite
Selecting Treatment

- Side effect profile
- Cost
- FDA approval
- Efficacy (patient specific)
- Tolerability (patient specific)
Atypical Antipsychotics

- Acute EPS & Tardive Dyskinesia
  - Lower risk overall

- Prolactin Elevation
  - Risperidone (>6mg/day) >> all the others
  - Paliperidone (Invega) same as Risperidone

- Anticholinergic Effects
  - Olanzapine & Clozapine >>> others

- Orthostasis
  - Clozapine > Risperidone >>> others

- Sedation
  - Clozapine >> Quetiapine> Olanzapine>> others

- Cardiac Effects:
  - Clozapine associated with cardiomyopathy and myocarditis

- QTC prolongation:
  - Ziprasidone (Geodon) – 10 msec
Atypical Antipsychotics

Metabolic Abnormalities Chief Concern

- Weight gain + lipid abnormalities + potential precipitation/aggravation of DM

- All patients require monitoring:
  - Personal/Family History: Baseline & Annual
  - Weight (BMI): Baseline, Q 4 weeks, then quarterly; if 5% of more over baseline, consider switch; Waist circumference: Baseline & Annual
  - BP and FBG: Baseline, 12 weeks, then annual
  - Fasting Lipids: Baseline, 12 weeks, then annual if any elevation
Treating Persons with Bipolar Disorder

- Careful history with documentation of history of mood cycling and response to medications
- Educate patient about treatment strategies, pros and cons and how he/she can help you determine best, individualized treatment recommendations
- Be knowledgeable about AE and monitor accordingly
- Help your patient assess tolerability and efficacy of drug therapy as it relates to their symptoms
- Develop a self-rescue plan for early intervention during mood cycling, as needed
- Offer hope and encouragement for improving their ability to manage their mood disorder
Thank You!