Bipolar Disorder
A PRIMER ON BIPOLAR DISORDER FOR PRIMARY CARE

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Objectives: Bipolar Disorder Presentation

- To provide overview of Bipolar Disorder including prevalence, symptoms and course.
- Discuss the challenges faced when diagnosing a mood disorder
- Provide review of common conditions found to be co-morbid with Bipolar Disorder
- To review current pharmacological and psychosocial approaches to the treatment of Bipolar Disorder
Introduction to Bipolar Disorder

- Bipolar Disorder is an illness characterized by pathologic mood elevation and nearly always depressive episodes.
- Correct diagnosis is important:
  - See substantial M/M if untreated
  - Treatment differs from that of unipolar depression
- Family members, friends may help to reconstruct past episodes of mania/depression.
Bipolar Prevalence

- Depends on Source:
  - National Comorbidity Study: 1.6%
  - WHO: 2.1%
  - Judd /Akiskal: 6.4%
  - Several smaller reports-as high as 10%!
Bipolar Disorder: Untreated vs Treated Mortality Ratios

- Neoplasm
- CardioV
- CerebroV
- Accidents
- Suicide
- all causes

Mortality Ratios:
- untreated
- treated
Suicide

- Sig reduced life expectancy - 25-50% attempt suicide - significantly more than in depression
- 15% die by suicide
- Risk factors for suicide include:
  - Personal/family hx of suicidal behavior
  - Severity/number of depressive episodes
  - Alcohol/substance use
  - Level of pessimism
  - Level of impulsivity/aggression
  - Younger age of onset
A Diagnostic Challenge

- Misdiagnosed: 69%
- Times misdiagnosed: 3.5
- MD’s consulted before diag: 4.0
- Misdiagnosed as:
  - Unipolar Depression: 60%
  - Anxiety Disorder: 26%
  - Schizophrenia: 18%
  - Borderline PD: 17%
- 10% of suicides saw a PCP the day before
Diagnostic Criteria

- DSM emphasizes polarity
- No manic episode = no Bipolar Disorder
- Key diagnostic feature is cycling mood not absolute polarity
DSM Criteria

- Bipolar Disorder is a mental illness characterized by the presence of one or more of the following:
  - Manic Episode (Bipolar I)
  - Mixed Episode (Bipolar I)
  - Hypomanic Episode (Bipolar II)

- Only one of these episodes needs to occur just once during the lifetime of an individual in order for that individual to be considered as suffering from Bipolar Disorder.

The presence of a Major Depressive Episode is very common in the lifetime of individuals with Bipolar Disorder (more 90% of these individuals have at least one Major Depressive Disorder in their lifetime), but it is not necessary. There are individuals with Bipolar Disorder who do not have a history of Major Depressive Episodes in their lifetime.
Definitions

- **Manic Episode** - a distinct period of an abnormally and persistently elevated, expansive or irritable mood lasting for at least one week, or less if a patient must be hospitalized.”

- **Hypomanic Episode** - lasts at least 4 days and is similar to a manic episode but is not sufficiently severe to cause impairment in social/occupational functioning—and no psychotic features are present.
## Mania vs Hypomania

<table>
<thead>
<tr>
<th></th>
<th>Mania</th>
<th>Hypomania</th>
</tr>
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<tbody>
<tr>
<td>Inflated self esteem</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical/mental over-activity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Over involvement in pleasureable activities</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Possibly</td>
<td>Never</td>
</tr>
<tr>
<td>Results in hospitalization</td>
<td>Possibly</td>
<td>Never</td>
</tr>
<tr>
<td>Lasts less than 7 days</td>
<td>No</td>
<td>Possibly</td>
</tr>
<tr>
<td>Lasts less than 4 days</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Longitudinal Pattern: Bipolar I

- Euthymic
- Manic
- Cycling
- Depressed
How Does the Bipolar I Patient Present?

- Depressed
- Manic
- Cycling
Longitudinal Pattern: Bipolar II

- Depressed
- Euthymic
- Hypomanic
- Cycling
How Does the Bipolar II Patient Present?

- Depressed
- Hypomanic
- Cycling
Interpretation of a Depressive Episode

- Is your depressed patient’s mood bipolar?
- Is your depressed patient’s mood unipolar?
- **Unipolar depression is a diagnosis of exclusion**
## Unipolar or Bipolar?

<table>
<thead>
<tr>
<th></th>
<th>Unipolar</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Teens to 20’s</td>
<td>Pre-puberty</td>
</tr>
<tr>
<td><strong>Duration of Dep Episode</strong></td>
<td>Months/years</td>
<td>Weeks to several months</td>
</tr>
<tr>
<td><strong>Freq of Dep Episodes</strong></td>
<td>1-3 times/year</td>
<td>Same-or-Many more if rapid cycling</td>
</tr>
<tr>
<td><strong>Seasonality</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>+FH of mental Illness</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Postpartum onset</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Multiple Rx Failures</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Responds to many meds – for short time only</strong></td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Medical Co-morbidities: The Rule-Not the Exception

- Diabetes
- Obesity
- Cardiovascular
- Pain
- Migraine
- Substance Dependence

Co-morbidity
Differential Diagnosis

- Cancer
- Epilepsy
- AIDS
- Medications (e.g., antidepressants can propel a patient into mania; other medications may include baclofen, bromide, bromocriptine, captopril, cimetidine, corticosteroids, cyclosporine, disulfiram, hydralazine, isoniazid, levodopa, methylphenidate, metrizamide, procarbazine, procyclidine)
- Cyclothymic disorder
- Oppositional defiant disorder (in children)
- Substance abuse disorders (e.g., with alcohol, amphetamines, cocaine, hallucinogens, opiates)
Differential Diagnosis cont

- Anxiety Disorders
- Cushing Syndrome
- Head Trauma
- Hyperthyroidism
- Hypothyroidism
- Multiple Sclerosis
- Migraine Headache
- Neuro-syphilis
- Pediatric ADHD
- PTSD
- Schizoaffective Disorder
- Schizophrenia
- Seasonal Affective Disorder
- Systemic Lupus Erythematosus
Psychiatric Co-morbidities in Bipolar Disorder

- OCD
- Panic d/o
- PTSD
- Social Ph
- Anxiety d/o
- Alcohol
- SUD's
- ADHD
While considering a Bipolar Diagnosis

- Do a thorough medical and psychiatric history given broad differential. Assess carefully for suicidality.
- Assess for signs of substance use-check urine tox
- Perform careful physical exam
- Perform appropriate lab test incl urine tox screen
- Consider other tests: EEG or MRI to rule out other causes
Bloodwork to consider-highlites

- CBC w diff: rule anemia as cause of depression
- ESR/CRP/ANA-check for underlying inflammatory/infectious process such as SLE
- Fasting glucose/HGA1C-rule out diabetes. May effect treatment choice (ie atypicals cause weight gain).
- Electrolytes
  - hyponatremia can lead to depression.
  - Low sodium can lead to increased lithium levels
- VDRL/HIV
Bloodwork cont.

- **Calcium**
  - Hypercalcemia and hypocalcemia-mental status changes
  - Hyperparathyroidism-with elevated Ca levels leads to depression

- **Thyroid Hormones**
  - Hyperthyroidism-mania
  - Hypothyroidism-depression (Rx with lithium can cause hypothyroidism-and increase cycling)

- **Creatinine and BUN**-treatment with lithium-can increase BUN/Cr
Pharmacotherapy
Consider options for pharmacotherapy

- First Line medications should be proven mood stabilizers:
  - Lithium, Valproate, lamotrigine
  - Choose mood stabilizer over antidepressant despite less favorable side effect/risk profile
- Failure to respond to monotherapy—may need to add atypical antipsychotic
Lithium Carbonate

- **Study**: lithium vs VPA vs combination
  - Lithium maintained stability for avg 15 months
  - VPA maintained stability for avg 8 months
  - Lithium + VPA-only slightly better (9 months)
  - Lithium is still gold standard
Some Facts about Lithium

- Only medication likely to be “anti-suicidal”
- Also good for impulsive/violent tendencies
- Thought to be neuro-protective: Increases arborization/connections between neurons-esp in hippocampus
- Time frame for efficacy is weeks to months-may work by increasing BDGF
- Don’t hear much about lithium-is generic
Lithium Monitoring

- Shoot for 0.8 to 1.2 mEq/L or higher for acute mania
- 0.8-1.0 mEq/L for maintenance
- Monitor kidney function (BUN/Cr)
- Monitor Parathyroid function (Ca)
- Monitor thyroid function (TSH)
- Lithium levels over 1.3 mEq/L gen not well tolerated:
  - Fine hand tremor
  - Confusion, Dizziness
  - Headache, EKG changes
  - Nausea/vomiting/diarrhea
  - Hypothyroidism
Depakote (Valproic Acid)

- Long considered equal to lithium in efficacy
- Tends to work for “atypical” or mixed mood states
- Maybe effective when lithium fails
- Blood levels assure therapeutic dose (80-125 mcg/ml)
- Side Effects include nausea, decreased platelets, diarrhea, tremor, weight gain, alopecia
Other Agents

- Neurontin, Topamax
  - don’t separate from placebo
- Abilify-recent study showing benefit at 5 weeks is lost at week 8.
Atypical Antipsychotics for Acute Mania

- Risperdal 5mg-50% respond by day 3
- Zyprexa 10-15 mg-also respond by day 3
- Abilify-benefit in first few days-then flat
- Sapharis-10mg po bid, response by day 4

Therefore-with Atypicals-if don’t see 50% response by week one-better consider alt. Rx
Pharmacotherapy for Bipolar Depression

- **Lamictal**- FDA approved for maintenance treatment only-not acute mania or depression
  - 4 studies showed no effect on Bipolar Depression-but one showed benefit
  - Serious rash associated with rapid dose escalation

- **Symbyax**- (Olanzapine-Fluoxetine)-FDA approved
  - At least one good study showed no sig diff bet Zyprexa alone and Zyprexa plus fluoxetine

- **Seroquel**- also works but many drop outs from SE (9% placebo, 16% 300mg, 26% 600mg)
Do Antidepressants play a role in the Treatment of Bipolar Disorder?
Is Rapid Cycling Iatrogenic?

- Step-BD, N=1742, 75 % Bipolar I
- 32% reported rapid-cycling pre-study
- 5% had rapid cycling after one year of Rx
- Patients who received antidepressants were 3.8 times as likely to have rapid cycling
- Strong data suggesting that antidepressants do cause rapid cycling
Relapse Following Antidepressant Discontinuation versus Continuation

- Place Bipolar group with breakthrough depression on antidepressant
- Those that remit, place in two groups:
  - Short-term anti-dep Rx (<6 months)
  - Long-term anti-dep Rx (> 6 months)
- 2/3 of Short term group relapsed
- 1/3 of Long term group relapsed
- Therefore—for this subset (about 10-15% of Bipolar pts), may want to maintain antidep
Antidepressant Adjunctive to mood stabilizer

- Were given Wellbutrin, Zoloft or Effexor
- 55% of patients flipped to mania/hypomania
- Only 16% had sustained response (1 year study)
- Wellbutrin was least likely to cause flip
- SSRI/SNRI-about equally likely to cause flip
Meta-Analysis-Bipolar Depression

- 18 studies, 4105 patients looked at
- Mood Stabilizer monotherapy:
  - Increased rate of response
  - Increased rate of remission
- Adding Antidepressant was NOT statistically superior to monotherapy
Maintenance Therapy
Lithium versus Lamictal

- Several studies in Archives of Gen Psychiatry:
  - **Lithium** superior to Lamictal for preventing mania
  - **Lamictal** superior to Lithium for preventing Depression

- Sev Studies showing benefit from Olanzapine, Abilify and Seroquel with mood stabilizer-therefore-COMBINATION THERAPY may be beneficial
  - used to be called “Polypharmacy” and still is by some managed care entities
## Tolerability

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<th>DRUG</th>
<th>WEIGHT GAIN</th>
<th>CNS</th>
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<th>DERM</th>
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<tr>
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<td>++</td>
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<tr>
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<td>++</td>
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<td>+++</td>
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<tr>
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<td>+/-</td>
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<td>0</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>LAMICTAL</td>
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<td>+++</td>
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<tr>
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Pharmacotherapy During Pregnancy
Pregnancy and Bipolar Disorder

- Stop medication-2/3’s relapse, 1/3 do not
- Don’t use:
  - VPA-Neural Tube Defects
  - Lithium-Ebstein’s Anomaly (1 in 20,000 without lithium exposure, 1 in 1000 with exposure). Also see Coarctation of the aorta and mitral atresia.
- Lamictal-category B
  - Better for depression-and since depression is common presentation-is very good choice
- Prenatal exposure to first and second generation antipsychotics:
  - No enhanced risk for major physical malformations (no studies address potential long-term psychologic/behavioral consequences)
  - Seroquel has lowest placental permeability
  - Latuda, a relatively new atypical-is category B
Clinical Pearls
Clinical Pearls

1. Bipolar I Disorder: 3X’s more likely to be seen depressed than hypomanic/manic
2. Bipolar II-39X’s more likely to be seen depressed than manic/hypomanic
   - Depression - main clinical issue - so think Lamictal, Seroquel, Symbyax
3. Rapid Cycling - Lithium not as good as VPA to prevent “kindling”
4. Bipolar Disorder with psychotic features-think atypical antipsychotic
6. Consider use of Mood Diaries
7. Patients like to be manic/hypomanic
8. Assume Non-compliance until proven otherwise
Questions ?
Thank You!