Bipolar Disorder: Diagnosis, Treatment Options and Outcomes

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What is bipolar disorder?

- **Julia**- a 28 year old female seeks treatment at the request of her parents for depression, impulsive decisions and out of control anger.

- **Nickii**- an 8 year girl with uncontrollable rage and psychotic symptoms.

- **Jake**- a 52 year old male with multiple hospitalizations for depression and mania.
What is bipolar or “manic depression”? 

- Unipolar depression: all lows 
- Bipolar is both ends of the spectrum 
- Severe mood swings 
- Classic form: periods of extreme depression to periods of exaggerated happiness or euphoria 
- Many shades of the illness in between the extremes 
- Episodic nature, chronic, variable course
What are the forms of bipolar disorder?

1. Bipolar I Disorder: 6 separate criteria sets
2. Bipolar II Disorder: 2 separate criteria sets
3. Bipolar Disorder NOS
4. Cyclothymic Disorder
5. Mood Disorder Due to General Medical Condition
6. Substance-Induced Mood Disorder
7. Multiple Specifiers For Most Types
DSM Criteria for Bipolar I D.O.

- Must have or had at least one episode of mania
- Some patients have had or will have a major depression
- Episodes can be depressive, manic or mixed
What is Mania?

The DSM Criteria:
- Period of abnormally elevated, expansive or irritable mood
- Lasts at least one week or less if hospitalized
- Inflated self esteem, grandiosity
- Decreased need for sleep
- More talkative, pressured speech
- Flight of ideas, racing thoughts
- Distractibility
- Increased goal-directed activity or psychomotor agitation
- Increased pleasure seeking with high potential for negative consequences
What is a Major Depressive Event?

- Depressed mood (irritable in children) and SIG-E-CAPS criteria
- S: suicidal ideation
- I: decreased interests
- G: excessive guilt (worthlessness, hopelessness)
- E: decreased energy
- C: decreased concentration
- A: appetite
- P: psychomotor retardation or agitation
- S: sleep disturbance
Bipolar Disorder and Psychosis

- Psychosis may be part of mania or depression
- Catatonia
What is Major Depressive Episode?

- Must last at least 2 weeks
- At least 5 of criteria with one including depressed mood or decreased interests
What is Bipolar II D.O.?

- Must have or had one or more episodes of MDD
- Must have or had at least one episode of hypomania
- Never had a manic episode
What is Hypomania?

- Like mania, just less severe
- Period of elevated, expansive or irritable mood
- At least 4 days
- Not severe enough to cause marked impairment or require hospitalization, no psychotic features
What is Cyclothymic D. O.?

- 2 years minimum (1 year in children)
- Numerous periods of hypomania
- Numerous periods of depression but not MDD
Differences in Disorders

- Euthymic
- Bipolar I
- Bipolar II
- Cyclothymic
Task Force Recommendations

- International team of experts
- Expanding diagnostic criteria for several subtypes
- Add pediatric category
- Bipolar II: not “soft bipolar”
- Add ultra-rapid cycling specifier
- Not over diagnosed
- A spectrum disorder with sub threshold symptoms
- Use of diagnostic tools increase accuracy of diagnosis
Epidemiology

- Bipolar I: 0.8%, M=F (All forms: 2.6%)
- Bipolar II: 0.5%, F>M
- Across cultures, races
- Age of onset: 21 years
- M: first episode likely to be mania
- W: first episode likely to be depression
- 2/3 affected have close family member affected
- One parent: risk to child 15-30%
- Two parents: risk to child 50-75%
**Course of Disease**

- First episode may be mania, hypomania, depressive or mixed.
- First episode may be followed by symptom-free years
- Associated with substance abuse, truancy, recklessness, impulsivity, antisocial behavior
- Variability is hallmark of illness
- Chronic illness
- No cure
- Very treatable
- Suicide completion rate is high: 1 in 5 (M>F)
Course of Disease

- Depression as part of bipolar increased if:
- Earlier onset < 25 y. o.
- 5 or more spells of MDD
- Family hx of bipolar
- Atypical depressive symptoms
Cost of Bipolar Disorders

- $45 billion annually: direct and indirect costs
- Bipolar pt/yr: $3415
- Diabetes pt/yr: $2570
- General medical outpatient/yr: $1462
- Unemployment rate: up to 60%
- 6th leading cause of disability in world
- Delay in diagnosis increases costs
Comorbid Conditions

- Substance abuse
- Anxiety disorders: OCD and Panic Disorder
- ADHD
Treatment Approaches

Acute phase:
- Hospitalization at times
- Medication
- Education: patient and family
- Psychotherapy
Treatment Approaches

Preventative/maintenance phase:
- Noncompliance is common
- Two or more episodes mania/depression = life long medication
- Maintain regular sleep and daily patterns
- Do not use drugs/alcohol
- Reduce stress
- Recognize early warning signs
- Don’t abruptly stop meds-talk to your doctor
- Enlist support of family/friends
Treatment Goals

- Assess and treat acute exacerbations
- Decrease distress
- Improve functioning between episodes
- Prevent recurrences
- Provide support and insight to patient and family
Now, let’s get to the meds

- Lithium: antimanic effects discovered in 1949, used extensively since 1960’s
- Anticonvulsants: effects discovered in 1970’s
- Antipsychotics: atypicals and typicals
- Clozapine
Lithium (Eskalith, Lithobid)

- Generic available
- 900-2400 mg/day
- QD or BID
- Check serum levels: 0.6-1.5 mEq/L
- Check serum levels: Day 3-4, 1 mos, 3-6 mos, dose change
- Labs: CBC, renal, lytes, U/A, TSH, pregnancy test, ECG
Lithium (Eskalith, Lithobid)

Side effects:
- Acne
- Renal dysfunction
- Cognition
- Diarrhea, GI distress
- Hypothyroidism
- Polyuria, polydipsia
- Tremor
- Weight gain
- Sedation

Drug interactions:
- ACE inhibitors
- Diuretics
- NSAIDs
- Theophylline
- Caffeine
Valproate (Depakote)

- 750-2000mg/day
- Q hs or BID
- Labs: LFTs, CBC, Cr, BUN, pregnancy test
- Check serum levels: 50-150mcg/ml
- Check serum levels: 1-2 weeks, then 3-6 months, dosage change
Valproate (Depakote)

Side effects:
- Alopecia
- Ataxia, tremor
- Cognitive impairment
- Dizziness
- GI upset
- Liver and platelet dysfunction
- PCO
- Weight gain
- Sedation
- Rash

Drug interactions:
- Antipsychotics
- Benzodiazepines
- Carbamazepine
- Lamotrigine
- Lithium
- MAOIs
- Phenytoin
- TCAs
- Warfarin
Carbamazepine (Tegretol)

- Generic available
- 400-1600mg/day
- BID or TID
- Labs: CBC, LFTs, pregnancy test
- Check serum levels: 4-12 mcg/ml
- Check serum levels: day 5-7, weekly ‘til stable, 3-6 months
Carbamazepine (Tegretol)

Side effects:
- Ataxia
- Diplopia, nystagmus
- Dizziness
- Dysarthria
- GI upset
- Hyponatremia
- Leukopenia
- Rash
- Sedation

Drug interactions:
- Induces own metabolism
- Antipsychotics
- Benzodiazepines
- Cimetidine
- Corticosteroids
- Valproate
- Erythromycin
- Lamotrigine
- OCP
- TCA
- Warfarin
Lamotrigine

- Generic available
- 200mg/day
- Titrate slowly
- QD or BID
- Labs: renal, LFTs, pregnancy test
Lamotrigine

Side effects:
- Ataxia
- Dizziness
- Headache
- Nausea
- Serious rash-Stevens Johnson Syndrome
- Sedation

Drug interactions:
- Carbamazepine
- Valproate
Recent Advisory for Mood Stabilizers

- All current antiepileptics pose increase risk of suicidality
- Patients should be warned
- No black box advisory
- Included carbamazepine, oxcarbazepine, valproate among others
Risperidone (Risperdal)

- 1993
- 1-8mg daily
- Only depot form of atypical
- Depot form q 2 weeks
- Weight gain, sedation and high prolactin most common
- Above 6 mg daily - EPS
Olanzapine (Zyprexa)

- 5-20mg daily
- Very sedating
- Excessive weight gain
- Metabolic syndrome
Quetiapine (Seroquel)

- 300-800 mg daily
- Moderate for weight gain
- Slit lamp eye exam recommended - cataracts, not often done
- Very sedating
Ziprasidone (Geodon)

- 40-160mg daily
- 2001
- Short acting injectable available
- Can be used for acute agitation
- More weight neutral than other atypicals
- Lower incidence of metabolic syndrome
Aripiprazole (Abilify)

- 10-30mg daily
- “Dopamine stabilizer”
- Agonist in areas of low activity
- More weight neutral
- Low incidence of metabolic syndrome
Clozapine (Clozaril)

- 25-900mg daily
- 1989
- Weight gain
- Agranulocytosis - serious, fatal
- Weekly WBC count
- Specific protocol - complex to manage
- Used in refractory cases
- Seizures
- Excessive salivation
Atypical Antipsychotics

- How we choose:
  - Side effect profile - make them work for patient
  - Any absolute contraindications or medical risks
  - Other meds: drug-drug interactions
  - Cost!!!
  - Insurance
  - Patient/family perceptions
  - Doctor’s own perceptions about meds
General Side Effects of Atypicals

- Less likely to cause EPS or TD
- Prolactin elevation-galactorhea, gynecomastia
- Sedation
- Anticholinergic
- Weight gain
- Also seen with typicals
Are Atypicals Worth It?

- CATIE-Sept 2005
- NIMH study in NEJM
- Ground breaking
- Outcome stated typicals=atypicals in efficacy
- Cost of atypicals may not always be justified
- Patients stopped both meds at a high rate
## Cost of Meds

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical monthly cost</th>
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<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>$500</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>$400</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>$400</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>$200</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>$300</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>$400</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>$350</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>$45</td>
</tr>
<tr>
<td>Perphenazine (Trilafon)</td>
<td>$25</td>
</tr>
</tbody>
</table>
Texas Medication Algorithm Project (TMAP)

- Facilitate clinical decision making
- Using latest data, updated 2004
- Specific treatment sequences in general
- Specific treatment options to use in given patient
- Goal is full remission
- Increase compliance, patient education
## Treatment for Bipolar Mania/Mixed

### Stage One

<table>
<thead>
<tr>
<th>Euphoria</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>Valproate</td>
</tr>
<tr>
<td>Valproate</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Ziprasidone</td>
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<tr>
<td>Risperidone</td>
<td>Ziprasidone</td>
</tr>
</tbody>
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**Olanzapine and carbamazepine are 2nd tier due to side effect profile**

- **Nonresponders** - try alternate monotherapy
- **Partial response + good tolerability** = move to combo treatment
Stage Two (Combo therapy)

- Add lithium, valproate, atypical antipsychotic
- Pick 2
- Not 2 atypicals
- Not clozapine (no data)
- Not aripiprazole (no data)
- Nonresponders or partial responders: stage 3
Stage Three (Combo therapy)

- Combinations of 2 different drugs from more choices
- Lithium, valproate, atypicals, carbamazepine, aripiprazole, oxcarbamazepine, typicals
- Not 2 atypicals
- Not clozapine
- Nonresponders/partial responders go to stage 4
Stage Four

- ECT
- Add clozapine (to lithium and/or anticonvulsant)
Treatment for Bipolar Depressed

Stage One

- If on lithium: optimize blood level
- If on other antimanic, add lamotrigine
- If on no antimanic, no history of mania: lamotrigine
- If on no antimanic with severe hx, follow 1st protocol for mixed/mania
- Partial/nonresponders go to stage two.
Stage Two

- Try quetiapine monotherapy
- Or olanzapine/fluoxetine combo
- Partial/nonresponders go to stage three
Stage Three

- Combination of any two:
  - Lithium
  - Lamotrigine
  - Quetiapine
  - Olanzapine/fluoxetine combo
  - Not 2 atypicals
  - Partial/nonresponders go to stage four
Stage Four

- ECT
- Combination of lithium, quetiapine, lamotrigine, olanzapine/fluoxetine
  PLUS
- Venlafaxine or
- Buproprion or
- SSRI
- Can induce mania
- Partial/nonresponders go to stage five
Stage Five

- Limited empirical support
- Adverse effects
- MAO-I
- TCAs
- Stimulants
- Thyroid supplementation
- Oxcarbazepine
- Inositol
- Never 2 SSRIs, 2 TCAs, 2 AAP
Bipolar Knows No Boundaries

- Kurt Cobain
- Jane Pauley
- Sinead O’Connor
- Winston Churchill
- Handel
- Keats
- Van Gogh
- Patty Duke
- Teddy Roosevelt
- Ted Turner
- Charles Dickens
References

- Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision, American Psychiatric Association, 2000
- Physicians Desk Reference, 2008
- NIMH, Questions and Answers about the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE), http://www.nimh.gov/healthinformation.catieqa.cfm