Overview

- DSM-IV Bipolar Mania
- Clinical presentation and epidemiology
- Examine the similarities with other disorders
- Define the distinguishing characteristics
- Treatment options why studies were necessary
- Outcome
DSM-IV Mania
- 1 week period of elevated expansive irritable mood
- 3 or 4 of the following symptoms
  - inflated self-esteem or grandiosity
  - decreased need for sleep
  - more talkative/pressured to speak
  - flight of ideas, racing thoughts

Clinical Presentation Mania
- Happy, elated
- Delusions- firm beliefs that fail to follow the laws of logic and are acted upon
- Feel they are above the law, beyond consequences
- High activity levels
- Hypersexuality

DSM-IV Mania
- Distractibility
- Increase in goal directed activity or psychomotor agitation
- Excessive involvement in pleasurable activities

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Clinical Presentation Mania
- More likely to be delusional and have hallucinations
- Younger: irritable, labile, dysphoric, agitated
- Older: euphoric, elation, paranoid, grandiose delusions

Epidemiology Mania
- Prevalence similar to adult rates (0.6%-1%), rare
  <0.5% under age 10; 1-2% over age 10
- 20%-40% adult bipolar patients report childhood onset
- First episode usually M.D.D.
- Childhood onset M.D.D. switch to pre-pubertal mania 32%
- Adolescent onset M.D.D. switch to mania 20%, M:F 1:1 bipolar & unipolar 1:2

Comorbidity Mania
- ADHD 90% pre-pubertal, 30% adolescent bipolar subjects have ADHD
- Conduct disorder- 22% bipolar children; 18% bipolar adolescents
- Substance Abuse
- Anxiety 33% pre-pubertal, 12% bipolar adolescents
Overlapping Diagnostic Criteria

<table>
<thead>
<tr>
<th>ADHD</th>
<th>GAD</th>
<th>Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>Restlessness</td>
<td>Increased motor activity</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>Poor concentration</td>
<td>Distraictibility</td>
</tr>
<tr>
<td>Increased motor activity</td>
<td>Irritability</td>
<td>Irritability</td>
</tr>
<tr>
<td>Distraction</td>
<td>Irritability</td>
<td>Irritability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression</th>
<th>CD/ODD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor concentration</td>
<td>Irritability</td>
</tr>
</tbody>
</table>

Similarities
- Restless, impulsive, inattentive
- Poor peer interactions
- Trouble at home and at school following the rules, but ADHD kids act without thinking while manic kids act knowing it is wrong but feeling the rules do not apply to them
- The helicopter sign
- Academic performance poor
- Comorbid conduct/disruptive behavioral symptoms

Distinguishing Characteristics
- **MANIA**
  - acute onset impulsivity, motor restlessness, inattention
  - rare prepubertal 0.5% recent deterioration school and social, new onset disruptive behavior 22% prepubertal, 18% adolescent mania
  - positive family hx bipolar rate 1.5-10.2% 1st degree
- **ADHD**
  - chronic impulsive, restless, inattention over long period of time
  - must have onset before age 7, chronic school and social problems 30% comorbid disruptive behavioral disorders
  - positive family hx ADHD 10-35%, mood disorder 26%
Distinguishing Characteristics

- Euphoric or irritable, delusions of grandeur or paranoia, auditory or visual hallucinations, pressured tangential speech, internally distracted
- Decreased need for sleep with no fatigue or tiredness
- Marked increase or decrease in appetite with weight change
- ADHD symptoms, affect variable, no delusions or hallucinations, speech rapid but able to interrupt and not tangential, less internally distracted
- No decreased need for sleep, frequent initial insomnia and difficulty settling
- Similar growth pattern over time, unable to sit still to eat, anorexia 2→ to stimulants

Distinguishing Characteristics

- New onset boundless energy
- Stimulants may ↑ or ↓ symptoms, manic episodes precipitated in kids on stimulant and SSRI combination
- Mood stabilizer will improve symptoms in 3 weeks or more
- Long-term pattern of high purposeless energy
- 75-90% improve on stimulants, response is rapid
- Mood stabilizers not effective in improving ADHD symptoms

Cardinal Symptoms

- B Geller JCAP 2002 differentiate ADHD and pediatric bipolar disorder (PEA-BP) in clinical samples
- Elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, and hypersexuality
- Irritability, hyperactivity, accelerated speech, and distractibility were very frequent in both PEA-BP and ADHD groups

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Positive Trials

Olanzapine in Pediatric Bipolar Disorder

**Methods**

- N = 161, 10-17 y.o.
- Bipolar I disorder, mixed or manic, +/- psychosis
- YMRS ≥ 20
- 3 week double-blind placebo-controlled
- Start OLZ 2.5-5.0 mg/day, increase by same until 10-20 mg/day


### Olanzapine in Pediatric Bipolar Disorder

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender - Male, n (%)</td>
<td>61 (57%)</td>
<td>24 (44%)</td>
<td>.14</td>
</tr>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>15.1 (1.3)</td>
<td>15.4 (1.2)</td>
<td>.25</td>
</tr>
<tr>
<td>Race - Caucasian, n (%)</td>
<td>71 (66%)</td>
<td>41 (76%)</td>
<td>.25</td>
</tr>
<tr>
<td>Study Site - U.S., n (%)</td>
<td>95 (89%)</td>
<td>48 (89%)</td>
<td>1.00</td>
</tr>
<tr>
<td>YMRS (SD)</td>
<td>33.0 (6.5)</td>
<td>32.0 (8.2)</td>
<td>.35</td>
</tr>
</tbody>
</table>


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Olanzapine in Pediatric Bipolar Disorder

Results

<table>
<thead>
<tr>
<th>Olanzapine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completers, n (%)</td>
<td>85 (79%)</td>
<td>35 (65%)</td>
</tr>
<tr>
<td>YMRS Change</td>
<td>-17.7</td>
<td>-10.0</td>
</tr>
<tr>
<td>Responders</td>
<td>45%</td>
<td>46%</td>
</tr>
<tr>
<td>Remitters</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>CGI-BP change</td>
<td>-1.6</td>
<td>-1.0</td>
</tr>
</tbody>
</table>


YMRS Change from Baseline: Olanzapine vs. Placebo

Open Label Olanzapine Extension Study

- 146 subjects completing 3-week acute study
- Open label OLZ (2.5 mg - 20 mg) for up to 26 wks
- 63% response rate (50% reduction YMRS, CGI-BP Severity ≤ 3)
- Weight gain = 7.5 ± 6.8 kg
- ≥ 7% inc in weight = 69%
- Inc prolactin = 71%


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Risperidone in Pediatric Mania

Methods

- N = 166, 10-17 y.o.
- BD I, mixed or manic
- 3-week DBRCT
- Two doses of RIS (0.5 - 2.5 mg/day or 3.0 - 6.0 mg/day)

![Risperidone in Pediatric Mania](image)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.5-2.5 mg/day</th>
<th>3.0-6.0 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>19%</td>
<td>20%</td>
<td>42%</td>
</tr>
<tr>
<td>YMRS change, mean (SD)</td>
<td>9 (11)</td>
<td>19 (10)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>EPS</td>
<td>8%</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>Prolactin change, mean (SD)</td>
<td>Girls 0.6 (7)</td>
<td>Girls 32 (23)</td>
<td>Girls 50 (46)</td>
</tr>
<tr>
<td>Abnormal prolactin</td>
<td>0%</td>
<td>11%</td>
<td>26%</td>
</tr>
<tr>
<td>Weight change, mean kg (SD)</td>
<td>0.7 (1.9)</td>
<td>1.9 (1.7)</td>
<td>1.4 (2.4)</td>
</tr>
</tbody>
</table>

![Risperidone in Pediatric Mania](image)

Quetiapine in Pediatric Mania

Methods

- N = 277, 10-17 y.o. (Mean = 13.2 y.o.)
- BD I, manic
- Baseline YMRS = 30
- 3-week DBRCT
- Two doses of QUE (400 or 600 mg/day)
- 15% with adjunctive stimulant continued for ADHD

![Quetiapine in Pediatric Mania](image)

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**YMRS Change from Baseline: Quetiapine vs. Placebo**

Days: 0, 4, 7, 14, 21

- Placebo
- 400 mg
- 600 mg

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**Response Rates to Quetiapine**

- Day 4: 25%, 25%, 25%, 25%
- Day 7: 25%, 25%, 25%, 25%
- Day 14: 25%, 25%, 25%, 25%
- Day 21: 25%, 25%, 25%, 25%

- *p < 0.05, **p < 0.01; no p values displayed for other time points
- +50% YMRS total score improvement

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**Quetiapine Tolerability**

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>Quetiapine 400 mg</th>
<th>Quetiapine 600 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>28.4</td>
<td>31.6</td>
<td>10</td>
</tr>
<tr>
<td>Sedation</td>
<td>23.2</td>
<td>25.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18.9</td>
<td>17.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>1.7 kg</td>
<td>1.7 kg</td>
<td>0.4 kg</td>
</tr>
</tbody>
</table>

- NNH (>7% weight gain) = 9 for quetiapine vs. 3 for olanzapine

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Aripiprazole for Pediatric Mania

- N=302
- 10-17 y.o., BD I, manic or mixed
- 4-week DBPCT
- Randomized 1:1:1 to placebo: 10 mg: 30 mg

Dosing Schedule | Day
---|---
Low Dose, mg/day | 2 5 10 10 10 10
High Dose, mg/day | 2 5 10 15 20 25 30


Aripiprazole for Pediatric Mania

Results

- Baseline YMRS = 30.1
- Decrease in YMRS:
  - Placebo: 8.2, 10 mg = 14.2, 30 mg = 16.5,
- 50% drop in YMRS:
  - Placebo = 26%, Low dose = 45%, High dose = 64%
- Side effects: Akathisia (2%/9%/13%), weight gain (.5 kg/.6 kg/9 kg - NS)
- 4.6%, 4%, 12.3% with ≥ 7% gain in body weight


Primary Endpoint:
Mean Change in YMRS Score (LOCF)

Weeks of Treatment

Baseline YMRS score = 30.1


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Response Rate (LOCF)

Weeks of Treatment

* p < 0.05, ** p < 0.0001

YMRS Changes with Atypical Antipsychotics

YMRS Mean Change from Baseline

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Negative Studies for Bipolar

- Wagner AJP 2006 163(7)
- 116 6-17 bipolar mixed or manic, 7 weeks 57 PBO or 59 OXC 900-2400 mg/d
- Change in YMRS PBO 9.79, OXC 10.9
- Dropout due to AE PBO 4%, OXC 19%

Negative Studies for Bipolar

- Wagner JAACAP 2009 48(5)
- 4 week trial of 151 10-17yo PBO 74 VPA 77 concentration 80-125μg/ml
- Reduction in YMRS PBO 7.9 VPA 8.8
- Drop out for AE’s PBO 3, VPA 4
- Long term open label of 54 on VPA drop YMRS 2.2 points

FIGURE 2. Weekly Overall Adjusted Mean Change in Young Mania Rating Scale Scores of Subjects in a Multicenter, Randomized, Placebo-Controlled Trial of Oxybutynin in the Treatment of Children and Adolescents with Bipolar I Disorder Who Completed at Least One Efficacy Assessment

* The efficacy analysis used the last-observation-carried-forward method.

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**Outcome Mania**

- 17% adolescent onset recovered, 50% poor outcome
- Weiner et al, 1979- adolescent onset social disability, substance abuse, multiple suicide attempts and completed suicide
- Carlson, 1977- 60% good outcome; 20% impairment; 25% chronically ill
- Strober, 1990- compliance with lithium led to fewer relapses

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Questions?