Bipolar Disorders: Therapeutic Options

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Part 1: Overview and Treatment of Acute Mania
Teaching Points

1. The concept of bipolar disorder extends beyond DSM-IV.
2. Over time, most bipolar patients require combination therapy.
3. Treatment guidelines and algorithms abound.
4. There are 10 FDA-approved drugs for treating acute mania. There is no clear “winner”.

Outline

I. DSM-IV Bipolar Disorders Classification
II. The Bipolar Spectrum Concept
III. General Treatment Principles
   A. Improving Adherence
   B. Role of Psychotherapies
   C. Choosing Medications
   D. Combination Therapies
IV. Guidelines and Algorithms
V. Pharmacotherapy of Acute Manic and Mixed Episodes
   A. FDA-Approved Drugs
   B. Supportive Data for Efficacy
   C. Texas Implication of Medication Algorithm (TIMA)
Pre-Lecture Exam

Question 1

1. All of the following are FDA-approved for treating acute mania except:
   a. Carbamazepine
   b. Clorpromazine
   c. Clonazepam
   d. Divalproex
   e. Aripiprazole
2. A patient with a history of hypomanic episodes and major depressive episodes would receive which DSM-IV diagnosis?

a. Cyclothymic disorder
b. Bipolar NOS
c. Bipolar I
d. Bipolar II
e. Bipolar III
Question 3

3. Which of the following drugs has a recommended starting dose for acute mania of 25 mg/kg/day?
   a. Divalproex ER
   b. Carbamazepine ER
   c. Risperidone
   d. Divalproex
   e. Quetiapine
Question 4

4. Why is olanzapine not listed in Stage IA of the TIMA algorithm for acute mania monotherapy?
   a. Issues about efficacy
   b. Safety and tolerability
   c. Cost
   d. Complexity of use
Mood Disorders: DSM-IV Classification

DSM-IV Mood Disorders

Depressive Disorders
- Dysthymic Disorder
- MDD
- Depressive Disorder NOS

Bipolar Disorders
- BD-I
- BD-II
- BD-NOS
- Cyclothymia

Substance-induced

Due to General Medical Condition

Bipolar Disorders: DSM-IV

- Bipolar I disorder
  - Hypomaniac, manic, mixed, depressed, unspecified
- Bipolar II disorder
- Cyclothymic disorder
- Bipolar disorder NOS (not otherwise specified)
### Bipolar Lifetime Prevalence Rates

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Studies</th>
<th>Range of Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD-I</td>
<td>19</td>
<td>0.0-2.4</td>
</tr>
<tr>
<td>BD-II</td>
<td>10</td>
<td>0.3-2.0</td>
</tr>
<tr>
<td>Cyclothymia</td>
<td>5</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>Bipolar spectrum disorders</td>
<td>10</td>
<td>2.6-7.8</td>
</tr>
</tbody>
</table>

**BP-I: 0.8-1.6%, BP-II: 0.5-5.5%**

Mixed Bipolar Episode (DSM-IV)

- Criteria for both a major depressive episode and a manic episode
- For at least 1 week
Bipolar Spectrum Disorders

• Bipolar I disorder: history of mania*

• Bipolar II disorder: history of hypomania and major depressive episodes*

• Cyclothymia*

• Hyperthymic temperament

• Secondary mania (to other illnesses or drugs)

• Antidepressant-induced mania and hypomania

Hyperthymic Temperament*

• Extroverted and people-seeking
• High energy level
• Extremely sociable to the point of intrusive
• Overconfident, boastful and grandiose
• Stimulus seeking
• Short sleeper (less than 6 hours per night)

*Habitual long-term functioning of the individual;
Akiskal HS (1996), J Clin Psychopharmacol 16(2 suppl 1):4S-14S
Bipolar Spectrum

Angst and Cassano. Bipolar Disord 2005;7(Suppl 4):4-12
Zurich Study Hypomania Criteria

Strict
3 or more DSM-IV criteria
Minimum duration 1 day
Consequences

Loose
2 or more DSM-IV criteria
No minimum duration
No consequences

Angst and Cassano. Bipolar Disorders 2005;7(suppl):4-12
General Treatment Principles

- Psychosocial interventions
- Pharmacologic interventions
- Promote education
- Enhance compliance
Improving Treatment Adherence

- Therapeutic alliance
- Education
- Availability and support
- Psychotherapy
- Medication -- minimize side effects, complexity, cost
Bipolar Psychotherapies

• Family Focused

• Interpersonal and Social Rhythm

• Cognitive-Behavioral

• Life Goals Program
Choice of Medication(s)

- Phase of illness
- Prior response and tolerability
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient preferences
Polypharmacy is Not a Bad Word

• Monotherapy is the exception
• Combination therapy is effective
• Increased risk of side effects and drug interactions
Algorithms and Guidelines

• Synthesize current evidence
• Add expert consensus
• Balance with safety and tolerability
• Not written in stone
Bipolar Guidelines Abound

- **APA Practice Guidelines** 2002
  Am J Psychiatry 2002;159(suppl):1-50 (April)
- **Br Assoc Psychopharmacol** 2003
  J Psychopharmacol 2003;17:149-173
- **Expert Consensus Guidelines** 2004
  Postgrad Med Special Report 2004 (Dec)
- **WFSBP Guidelines** 2004
- **CANMAT Guidelines** 2005
  Bipolar Disorders 2005;7(suppl 3):5-69
- **TIMA Algorithms** 2005
“All guidelines have similar objectives, but they often reach different conclusions.”

Vieta et al., Bipolar Disord 2005;7(Suppl 3):73-76
Acute Manic and Mixed Episodes
Opium

“... it calms and soothes the Disorders and Perturbations of the animal Spirits; which, when lulled and charmed by this soporiferous Drug cease their Tumults, and settle into a State of Tranquility”

Sir Richard Blackmore, 1725
Acute Mania: FDA-Approved

- 1970 Lithium
- 1973 Chlorpromazine
- 1995 Divalproex
- 2000 Olanzapine
- 2003 Risperidone
- 2004 Quetiapine
- 2004 Ziprasidone
- 2004 Aripiprazole
- 2004 Carbamazepine ER
- 2005 Divalproex ER
Acute Mania: Divalproex vs Lithium

(≥50% ↓ in Mania Subscale)

Bowden et al. JAMA. 1994;271:918-924
Divalproex vs. Lithium for Mania

Bowden et al. JAMA. 1994;271:918-924

Note: Y-axis does not begin at zero
Divalproex ER for Bipolar Disorder

- FDA-approved 12/05 for acute manic and mixed episodes
- Bioequivalent to divalproex at ER dose 8 to 20% higher
- Start 25 mg/kg/day (once daily)
- 250 mg and 500 mg tablets
- Target: 85-125 mcg/mL
Neuroleptics* plus Valproate or Placebo for Acute Mania

• European Valproate Mania Study Group (10 sites, 3 weeks, n=136)
  - VPA (20 mg/kg) > placebo
    - faster and better response (58% vs 30%)
    - lower neuroleptic dose
    - well tolerated

• What about VPA alone?

*Haloperidol or perazine

Atypical Antipsychotic + Mood Stabilizer (Lithium or Divalproex) for Acute Mania

• Effective vs. placebo (FDA-approved)
  – Olanzapine
  – Quetiapine
  – Risperidone

• Probably effective (pending studies)
  – Others

All Antipsychotic Drugs Are Antimanic

Name one that isn’t!
## Divalproex vs. Olanzapine for Acute Mania

<table>
<thead>
<tr>
<th></th>
<th>Tohen et al., 2002</th>
<th>Zajecka et al., 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start</strong></td>
<td>OLZ 15 mg</td>
<td>OLZ 10 mg</td>
</tr>
<tr>
<td></td>
<td>DVPX 750 mg</td>
<td>DVPX 20mg/kg/day</td>
</tr>
<tr>
<td><strong>MRS</strong></td>
<td>OLZ -13.4</td>
<td>OLZ -17.2</td>
</tr>
<tr>
<td></td>
<td>(p=.028)</td>
<td>(n.s.)</td>
</tr>
<tr>
<td></td>
<td>DVPX -10.4</td>
<td>DVPX -14.8</td>
</tr>
<tr>
<td><strong>↑ Weight</strong></td>
<td>OLZ &gt; DVPX</td>
<td>OLZ &gt; DVPX</td>
</tr>
</tbody>
</table>

## Olanzapine for Acute Mania
*(pooled analysis – 2 studies)*

<table>
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<tr>
<th>Outcome Description</th>
<th>OLZ</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (≥ 50% ↓ YMRS)</td>
<td>55%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Euthymia (YMRS ≤ 12)</td>
<td>50%</td>
<td>27%</td>
</tr>
<tr>
<td>Remission (YMRS ≤ 7, etc.)</td>
<td>18%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Aripiprazole in Acute Mania
(3-week, double-blind, start 30 mg)

Trial 1  Response Rates  Trial 3

Percent responders (≥ 50% YMRS decrease)

Placebo  Aripiprazole  Placebo  Aripiprazole


Data on file, Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd.
Quetiapine for Acute Mania

Trial 105-McIntyre et al., Eur Neuropsychopharmacol 15:573-585, 2005
Trial 105-Bowden et al., J Clin Psychiatry 66:111-121, 2005
Quetiapine vs. Divalproex in Adolescent Mania (4-week, double-blind, n=50)

- **QTP:** 400-600 mg/day (mean 412 mg)
  - DVPX: mean serum level 101 mcg/ml
- **YMRS change (primary outcome)**
  - QTP 23
  - DVPX 19 (n.s.)
- **Response (CGI-I-mania 1 or 2)**
  - QTP 72% (p=0.02)
  - DVPX 40%
- **Remission:** QTP 60%, DVPX 28% (p=0.02)

DelBello et al. J Am Acad Child Adolesc Psychiatry 2006;45:305-313 (March)
Risperidone in Acute Bipolar Mania

Change From Baseline in Total YMRS (Primary Efficacy Variable)

LOCF analysis. *P<.001 risperidone vs placebo.


Ziprasidone: Efficacy in Acute Mania

Mean Change From Baseline (LOCF)

Study Day

Placebo (N=66)

Ziprasidone (N=131)

Mean Change in MRS

* p<0.01;
Keck et al., Am J Psychiatry 2003;160:741-748

† ziprasidone = 26.19; placebo = 26.49; ‡ p<0.05;
Acute Mania: Monotherapy
TIMA Stage IA

- Euphoric: lithium, divalproex, aripiprazole, quetiapine, risperidone, ziprasidone
- Mixed: divalproex, aripiprazole, risperidone, ziprasidone (not lithium or quetiapine)

TIMA: Texas Implementation of Medication Algorithms
Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886
Why Not Lithium or Quetiapine for Mixed Episodes?

• Lithium-May be less effective for mixed

• Quetiapine: Mixed excluded from pivotal trials, so not FDA-approved

• Divalproex ER, but not divalproex: FDA-approved for mixed
Aripiprazole in Acute Mania
Manic and Mixed Episodes

Mean YMRS change from baseline

n= 158/167
Manic

n= 96/92
Mixed

* P≤0.001, † P=0.002; Pooled analysis of 2 pivotal studies.

Data on file, Otsuka America Pharmaceutical, Inc.

CONTAINS OFF-LABEL INFORMATION
Risperidone in Mania
Manic vs. Mixed Episodes

Khanna et al., Br J Psychiatry 2005;187:229-234
Ziprasidone in Dysphoric Mania: Mania Rating Scale Score

**The placebo line represents pooled placebo data; P values for haloperidol were calculated in comparison to placebo data only from 1 of 3 pooled studies; *p<0.001; Zajecka J et al. (2005), Presented at the 158th Annual Meeting of the APA. Atlanta, Georgia; May 2005**
Carbamazepine ER Reduces Manic Symptoms of Mixed Episodes

Pooled Analysis of YMRS Change (Mixed Episodes)\(^1\)

*\(P<.01\) compared to placebo following analysis of covariance with baseline score as covariate.

Acute Mania: Monotherapy
TIMA Stage IB

• Euphoric and mixed
  – Olanzapine, carbamazepine ER

• Both FDA-approved, why not Stage 1A?
  – Complexity of use and/or safety/tolerability

Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886
Consensus Development Conference (Weight Gain, Diabetes, Dyslipidemia)

• Clozapine, olanzapine  
  --Increased risk

• Quetiapine, risperidone  
  --Some risk

• Aripiprazole, ziprasidone  
  --Little or no risk

Carbamazepine-Drug Interactions
An Incomplete Listing

• CBZ decreases levels of:
  - Clonazepam, clozapine, olanzapine, haloperidol, alprazolam, bupropion, oral contraceptives

• CBZ levels increased by:
  - Cimetidine, macrolides, fluoxetine, valproate, isoniazid, verapamil, ketoconazole
Acute Mania: 2-Drug Combos
TIMA Stage 2

• Lithium, valproate, atypical antipsychotics

• But not aripiprazole, clozapine, 2 atypical antipsychotics

• Why not aripiprazole?
  – No combination trials yet

• Why not start at Stage 2?
  – Many clinicians do

Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886
Acute Mania: TIMA

• **Stage 3**: less established 2-drug combinations

• **Stage 4**: ECT, clozapine, 3+ drug combinations, etc.

Clozapine for Bipolar Disorder

• The ace in the hole

• Open label reports of benefit for mania, maintenance, and possibly depression

• No double-blind studies

Post-Lecture Exam

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b. Safety and tolerability
c. Cost
d. Complexity of use
Answers to Pre & Post Lecture Exams

1. C
2. D
3. A
4. B