The Bipolar Continuum: Mania, Depression and Mixed States

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Syndromes and Variations
DSM IV Manic Episode

A. Mood abnormally elevated, expansive or irritable for 1 week
B. At least 3 of the following for euphoric, 5 for irritable
   1. Grandiosity
   2. Decreased need for sleep
   3. Pressured speech
   4. Flight of ideas
   5. Distractibility
   6. Increase in goal directed activity
   7. Excessive pleasurable activity with painful consequences
C. Marked impairment in functioning
D. No delusions or hallucinations for as long as 2 weeks in the absence of prominent mood symptoms

American Psychiatric Association, 1994
Spectrum of Manic States

- **Normal States**
  - Happiness
  - Pleasure
  - Joy

- **Hypomania**
  - Over-confident
  - Talkative
  - Less sleep
  - Increased
  - Productivity
  - Questionable

- **Mania**
  - Grandiosity
  - Irritability
  - Distractibility
  - Hyperactivity

- **Dellirious or Psychotic Mania**
  - Agitation
  - Aggression
  - Hallucinations
  - Delusions

- **Collateral**
  - Biased historian
  - Good behavior in the office
Cluster Analysis of Mania

Subtypes based on SADS

Subsyndromal symptomatology
- After recovery (8 consecutive weeks in remission)

Prognosis of “roughening” at 4 weeks
- 25% of dysphoric patients will have a major depressive episode (MDE) within 4 weeks
- 67% of patients with hypomanic symptoms will be manic within 4 weeks.

Depression

- Unipolar and Bipolar Depression same criteria
  - DSM-IV Bipolar, Depressed
    “Currently in Major Depressive Episode (see p 327)”
    - Insomnia or hypersomnia
    - Decreased or increased appetite, weight loss or gain
  - Nominally only difference is history of mania
Bipolar vs. Unipolar Depression

Reversed vegetative features 5X’s more common

Akiskal HS, et al. JAD 5:115-128, 1983
Depressed 32% of the Time

NIMH Collaborative Depression Study
146 patients followed every 6 months over 12–20 years

- Euthymia: 52.7%
- Depression: 9.4%
- Dysthymia: 9.3%
- Subsyndromal: 13.5%
- Elevated: 8.9%
- Cycling: 5.9%

Judd LL et al. *Arch Gen Psychiatry.* 2002;59:530-537.
Time Spent Depressed, BP 1 vs. BP2

**NIMH Collaborative Study, 13 years**

**BPI**
- Depressions: mania 3:1

**BP II**
- Depression: mania 37:1
- Higher morbidity, chronicity

### Prepubertal Major Depression to Bipolar

<table>
<thead>
<tr>
<th>Prepubertal MDD (n = 72)</th>
<th>Normal Controls (n = 28)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I or II 48.6%</td>
<td>7.1%</td>
<td>.0001</td>
</tr>
<tr>
<td>Bipolar I 33.3%</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>Bipolar II 15.3%</td>
<td>7.1%</td>
<td>.34</td>
</tr>
</tbody>
</table>

- Comorbid ADHD or psychotic depression = study exclusion
  - Both exclusions lowered rates of bipolar outcome
- Mania in parent or grandparent predicted BPI outcome \( (P=0.02) \)

Conversion from Unipolar Depression to Bipolar

Conversion rate depends on onset, severity

- Prepubertal depressives, avg age 10.3<sup>2</sup> 49%
- Adolescents<sup>1</sup> 19-37%
- Adults, age 30’s<sup>1</sup> 5-10%
- Hospitalized depressives, age 23<sup>3</sup> 46%
- Hospitalized depressives<sup>4</sup>
  - Retro/pro, age 33.5 50%
  - Prospective only, age 47.9 39%

Risk of Bipolarity in Depressed Outpatients

Depressed outpts, n=744, mania Hx total sample 27%
- 0 indicators 15%
- 1 indicator 19-22%
- 2 indicators 45-55%
- 3 indicators 67%

Bipolarity Index Predicts Response

1. Episode characteristics
2. Family history
3. Age at onset
4. Course
5. Response to treatment

Sachs, GS, Acta Psychiatr Scand Suppl 2004 : (422);7-17
Population At Risk for Bipolar

- Depressed but never hypomanic
- Early age at onset
- Reverse vegetative symptoms
- Third generation affective disorder
- Relative with mania

*So what?*
Evolution of Early Onset Bipolar

Prospective LIFE, N=263, mean age 13, mean 2 years

- 25% BP NOS → BP 1 or 2
- 20% BP 2 → BP 1
- Youths
  - More time symptomatic
  - More mixed, cycling
  - More changes
  - More switches

Age at Onset and Morbidity

**STEP-BD, N=983, early onset predicts**

- More lifetime manias and depressions
  - More episodes past year
  - More likely to present depressed or mixed
  - Similar frequency of psychosis
- More comorbid conditions
- More suicide attempts (Onset <13, OR 2.85)
- Lower QOL but not functioning

After controlling entry age and illness duration

## Age at Onset and Relapse

Adult BP I or II, N=3,658, prospective up to 2 yrs

<table>
<thead>
<tr>
<th>Onset (Years)</th>
<th>Time to Relapse (Median days)</th>
<th>Depressed Relapse %</th>
<th>Days Well %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 13</td>
<td>308(^a)</td>
<td>74.4 %</td>
<td>42.0 %</td>
</tr>
<tr>
<td>13-18</td>
<td>418(^b)</td>
<td>74.1 %</td>
<td>47.1 %</td>
</tr>
<tr>
<td>&gt;18</td>
<td>542</td>
<td>72.1 %</td>
<td>54.0 %</td>
</tr>
</tbody>
</table>

\(^a\) vs. adult, \(p = .0001\)
\(^b\) vs. adult, \(p = .01\)

DSM IV Mixed Episode

A. Meets criteria for both Manic and Major Depressive Episode nearly every day for 1 week
   – Depression is all or most of the day
   – Mania can be brief, often episodic or circadian

B. Marked impairment in functioning

C. Not due to a substance or medical condition
# Rates of Mixed States

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winokur et al., 1969</td>
<td>61</td>
<td>16</td>
</tr>
<tr>
<td>Kotin &amp; Goodwin, 1972</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Himmelhoch et al., 1976</td>
<td>84</td>
<td>31</td>
</tr>
<tr>
<td>Akiskal &amp; Puzantian, 1979</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>Nunn, 1979</td>
<td>112</td>
<td>36</td>
</tr>
<tr>
<td>Secunda et al., 1985</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Prien et al., 1988</td>
<td>103</td>
<td>67</td>
</tr>
<tr>
<td>Post et al., 1989</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>506</td>
<td><strong>40.1</strong></td>
</tr>
</tbody>
</table>

From Goodwin & Jamison, 1990
Depressive vs. Manic Mixed States

Number of Symptoms

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Irritable Mania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoric Mania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mixed Hypomania

\(BD 1 \text{ and } 2, \, N=908\)

- 392 patients (43\%), 1044 hypomanic visits
- 277 (71\%) had at least one mixed visit
- BD 1 a/w more hypomanic visits
- Women broadly affected
- Men irritability, agitation

Hallucinations

Schizophrenia >> **Mixed** > Manic = Bipolar D > Unipolar D

61.1

Prevalence (%)

- Schizophrenia: 61.1%
- Bipolar mixed: 22.9%
- Bipolar manic: 11.2%
- Bipolar depressed: 10.5%
- Unipolar depressed: 5.89%
Symptom Severity

- Mania more variable
- Depression more persistent
- Peak together rather than alternating

Kotin and Goodwin, 1972
Mixed Symptoms and Suicide Attempt

- Mania score of only 6 in depressed patients a/w suicide attempts and alcohol abuse

<table>
<thead>
<tr>
<th>Sx</th>
<th>Manic</th>
<th>Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>2</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Early onset</td>
<td>Suicide attempt</td>
</tr>
</tbody>
</table>

Swann A. Bipolar Disord. 2007 May;9(3):206-12.
Typcial Mixed Picture

- Depressed and sluggish on awakening
- Struggles with morning routine
- Energy begins to pick up late morning
- Runs of racing thoughts
- Periodically restless, cleaning, errands
- Evening irritable, tired but anxious, distractible
- Bed but racing thoughts, can’t sleep
- Often do not meet criteria for mania
- Frequently associated with antidepressants
DSM IV Rapid Cycling

A. At least 4 episodes in 12 months that meet criteria for Major Depressive, Manic, Mixed or Hypomanic Episode

B. Episodes demarcated by full or partial remission for 2 months or switch to opposite pole
Rapid Cycling Life Chart

Lithium Prophylaxis in Rapid and Non-Rapid Cyclers

- Criteria for lithium nonresponse
  - Hospitalized or treated for depression or mania
  - Symptoms sufficient to warrant Dx of mild depression or hypomania for 2 weeks

Dunner & Fieve. *Arch Gen Psychiatry.* 1974;30:229-33.
Rapid Cycling as a Course Modifier: DSM-IV Work Group

- **Demonstrate validity as a distinct modifier**
  - Rapid cycling defined as ≥4 episodes in preceding year

- **Methods and Subjects**
  - 4-site pooled data reanalysis
  - Retrospective and prospective (>12 months)

- **Findings**
  - Rapid cycling is a distinct course modifier with differences in sex and outcome

### Prevalence of Rapid Cycling

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tondo et al.</td>
<td><em>Am J Psychiatry</em> 1998</td>
<td></td>
<td>24.2 %</td>
</tr>
<tr>
<td>10 studies, N = 2057</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coryell et al.</td>
<td><em>Arch Gen Psychiatry</em> 1992</td>
<td></td>
<td>18.5</td>
</tr>
<tr>
<td>Kukopulos et al.</td>
<td><em>Pharmakopsychiatr</em> 1980</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Dunner &amp; Fieve.</td>
<td><em>Arch Gen Psychiatry</em> 1974</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>
Rapid Cycling: 7 Definitions

1. DSM-IV definition
2. 4 or more episodes/yr, *episodes* > 2 *wks*
3. 4 or more episodes/yr, mood episode > 1 *wk*, 1 *week of euthymia*,
4. Like 1, but duration criteria waived for affective episode, requires *circular course*
5. 4 or more episodes/yr, each at least 24 hours, separated by 24 hours of euthymia or mood in opposite polarity
6. 4 or more episodes/yr of RDC defined mood separated by 2 *wks* of euthymia or switch
7. 4 or more episodes in any previous year, separated by switch or euthymia as long as proximate episode

Schneck C.
Rapid Cycling and Bipolar II

Rapid Cycling 6 times more common in Bipolar II

Prevalence 20%

- Younger age of onset
- Greater severity of illness on multiple clinical and functional measures

STEP-BD Rapid Cycling

- Women > men
- No association between RC and BPII
- More SUD in RC BPI
  43 vs. 18%

Female Predominance in Rapid Cycling

Women

100 % of S’s with ≥ 9 episodes

~80 % of S’s with 4-8 episodes

Factors Related to Rapid Cycling

Associated
Female (71%)
Major depression (84 vs 56%)
Hypomania (20 vs 9%)
Hypomanic cycling (20 vs 7%)

Not Associated
Antidepressants
Family history
Thyroid disease

Only 7% with mania at entry developed rapid cycling

Coryell et al, AM.J. Psychiatry 1992
Course of Rapid Cycling

State or Trait?

- 64% no rapid cycling after first year
- 18% rapid in year two but not subsequently
- **Only one cycled all five years**

Coryell et al, Arch Gen Psychiatry, 1992
Rapid Cycling or Circularity?

10 year prospective observation, N=194

- BP2 more common among polyphasics
  - 46.4 vs 25.8%
- Pattern frequently retained
  - 65% of depressives
  - 42% manics
- Mult switches predicted
  - Slower recovery
  - More time ill

RC in the Prior Year Predicts Cycle Frequency

STEP-BD 2000

- **RC Prior Yr**: 40% Stable, 30% 1 Episode, 12% 2-3 Episodes, 6% Rapid, 12% Dropped
- **No RC Prior Year**: 36% Stable, 19% 1 Episode, 3% 2-3 Episodes, 3% Rapid, 14% Dropped

p < .0001

Prepubertal, Early Adolescent Mania vs ADHD

All comparisons $p<.0001$

Prepubertal, Early Adolescent Mania vs ADHD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Bipolar (N=93)</th>
<th>ADHD (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Judgment</td>
<td>44.4</td>
<td>90.3</td>
</tr>
<tr>
<td>Irritable Mood**</td>
<td>71.6</td>
<td>97.9</td>
</tr>
<tr>
<td>Accelerated Speech</td>
<td>81.5</td>
<td>96.8</td>
</tr>
<tr>
<td>Distractibility</td>
<td>93.6</td>
<td>96.3</td>
</tr>
<tr>
<td>Increased Energy</td>
<td>100</td>
<td>95.1</td>
</tr>
</tbody>
</table>

* Adapted with permission from Craney & Geller. 11
*p = .002 for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.
**p < .001 for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.
Abbreviation: ADHD – attention-deficit/hyperactivity disorder.
Summary

*Tremendous variation*

- Many depressives have a Bipolar diathesis
  - Early onset marker for diagnosis and course
- Bipolar depression persistent, recurrent
- Cycling begets cycling
- Mixity is very problematic
- Subsyndromal states are important
  - Treat mania early and aggressively
Treating Bipolar Disorder
General Principles

**Multiphase Treatment Goals**

1. Symptomatic remission
2. Functional recovery
3. Prevention

*Fewest, briefest, mildest episodes*

Residual Symptoms and Relapse

Collaborative Depression Study, BP I/II, median 17yrs

- Median time to relapse
  - 24 weeks for residual
  - 123 weeks for asymptomatic

- Treat to recovery
  - Not random assignment
  - Resistance, relapse traits

Judd, L. Arch Gen Psychiatry. 2008; 65(4):386-394.

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General Principles

Initiation

Severity, medical and psychiatric comorbidity, suicidality
Evidence of efficacy and tolerability
   Literature and individual patient history
Patient preference
Involvement of significant others
Mood charting or other self monitoring
Visits at least every 2 weeks
Formal psychoeducation and cognitive therapy

Consider Prophylaxis for Future Episodes

Selection depends on next phase
- Classic euphoric mania
- Depressed or mixed
- Cycling
## “Like Breeds Like”

*Risk of Relapse to Same Polarity ~ 2:1 or 3:1*

<table>
<thead>
<tr>
<th>Index Episode</th>
<th>Relative Risk of Relapse to Index Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baastrup (1970)</td>
<td>1.6</td>
</tr>
<tr>
<td>Cundall (1972)</td>
<td>4.2</td>
</tr>
<tr>
<td>Stallone (1973)</td>
<td>1.4</td>
</tr>
<tr>
<td>Prien (1973a)</td>
<td>6.1</td>
</tr>
<tr>
<td>Prien (1973b, 1974)</td>
<td>2.6</td>
</tr>
<tr>
<td>Fieve (1976)</td>
<td>21.3</td>
</tr>
<tr>
<td>Dunner (1976)</td>
<td>.47</td>
</tr>
<tr>
<td>Bowden (2003)</td>
<td>1.5</td>
</tr>
<tr>
<td>Bowden (2003)</td>
<td>1.3</td>
</tr>
<tr>
<td>Calabrese (2003)</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Prien (1973a) Mania

Prien (1973b, 1974) Depression

Fieve (1976) Mania

Dunner (1976) Mania

Bowden (2003) Mania

Calabrese (2003) Depression

General Principles

*Continuation (4-6 months)*

Maintain acute treatments at least 2 weeks beyond first “response” to ensure stability
Continue effective treatments adjusting for tolerability
Discontinue least tolerable medications first
  - Gradual taper, 2-4 weeks minimum
Add medications for subsyndromal or comorbid symptoms
  - Overlap and taper
Visits at least monthly for 3 months, then q 2-3 months

General Principles

**Maintenance**

Continue effective acute phase treatment or
Switch to one with evidence of maintenance efficacy
Simplify medication regimen

- Improve tolerability and adherence
- Little data on combinations in maintenance

Treating Acute Mania
TIMA Bipolar 2005
Acute Mania

**Monotherapy**
- 6 first line “antimanics” rather than 3 “mood stabilizers”
- Valproate mentioned but divalproex better tolerated
- 4 AAP’s for euphoric mania (QTP and ZIP previously Stage 4)
  - 3 for mixed (no evidence on QTP in mixed mania)
- Olanzapine, carbamazepine separate stage due to safety, “complexity”
- No psychotic mania

Use targeted adjuncts before moving on

ARP = aripiprazole; CBZ = carbamazepine; CONT = continuation; Li = lithium; OLZ = olanzapine; OXC = oxcarbazepine; QTP = quetiapine; RIS = risperdone; VPA = valproate; ZIP = ziprasidone;

Mania, “More Severe”

*American Psychiatric Association, 2002*

| More Severe | VPA + (OLZ or RIS) or Li + (OLZ or RIS) BZD adjunct |

- Combinations indicated initially for severe mania
- Equivalent to Stage 2 in TMAP 2005
Antimanic Similar Effects

Pooled Drug Effects (random-effects model)

Difference in YMRS Change From Placebo (mean and 95% CI)

Perlis et al 2006. Dotted line on the left indicates pooled difference vs. placebo.
Predictability

Factors influencing response

- Substance use
- Mixed states
- Number of prior episodes
- Prior response
Speed

*Rapid titration, combinations*
- Depakote
- Risperidone, olanzapine, haloperidol

*Slower*
- Lithium slow, combinations more side effects
- Quetiapine titrated
Loading versus Titration

Linear Dose Response of VPA in Mania


Model Slope $p<.001$, Fitness 0.873, Jonckheere $p=.<.001$
Optimization

**Recommended levels/doses for mania**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Level/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium level</td>
<td>0.7 – 1.2 mEq/l</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>&gt;90 μg/ml</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>7 – 12 μg/ml</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>900 – 2100 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15 – 30</td>
</tr>
<tr>
<td>Clozapine</td>
<td>200 – 600</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 – 30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300 – 800</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.5 – 6</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80 – 180</td>
</tr>
</tbody>
</table>

QTP Titration Schedules

- SZP, PANSS ≥60, n=69
  - No significant baseline differences
- RDB, BID dosing
  - QTP 400 mg in 2 days
  - QTP 400 mg in 3 days
  - QTP 400 mg in 5 days
- 80-91% AE rate, mild-mod
- Withdrawals d/t agitation
  - 1 in 5 day, 2 in the 2 day group

Smith MA, …, Brecher M, et al, AstraZeneca
Risperidone plus MS for Acute Mania

*N=156, 70% Divalproex*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>-6.1</td>
<td>-8.4</td>
<td>-13.4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>-9.4</td>
<td>-11.5</td>
<td>-13.7</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td>-9.7</td>
<td>-10.5</td>
<td>-15.4</td>
</tr>
</tbody>
</table>

(YMRS Change)

- *P* 0.031 (Ris vs Plc)
- *P* 0.022 (Ris vs Plc)
- *P* 0.085 (Ris vs Plc)

\textbf{TIMA Bipolar 2005}

\textbf{Acute Mania}

\textbf{Stage 2}

\textit{Two-Drug Combination}\textsuperscript{b}

- \textit{Combinations (initial strategy for more severe mania)}
- Try more than one combination before moving on
- 2 anticonvulsants dropped
- 2 AAP’s not recommended
- No combination data with aripiprazole
- Clozapine appears later
- Oxcarbazepine was Stage 2, now Stage 3

\textsuperscript{b}\text{AAP = atypical antipsychotic; ARP = aripiprazole; CLOZ = clozapine; CONT = continuation; Li = lithium}

\textit{Li, VPA, AAP}
Choose 2 (not 2 AAPs, not ARP or CLOZ)

\text{Partial Response Or Nonresponse}

\text{Response}

\text{CONT}

\text{Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886}
Summary

Considerations

- Speed of acute behavioral onset
  - Rapid titration
  - Combinations
- Future prophylaxis
- Chronic tolerability
Treating Acute Bipolar Depression
TIMA Bipolar 2005
Acute Depression

Stage 1

Taking Li
Increase to $\geq 0.8$ mEq/L

Other Antimanic (continue)

No Antimanic, Severe or Recent Mania

No Antimanic, No Severe or Recent Mania

Antimanic + Lamotrigine

Lamotrigine

- Lamotrigine not antimanic
- If history of recent or severe mania, add or optimize antimanic
- Otherwise, lamotrigine monotherapy may be appropriate

TIMA Bipolar 2005

- Designed to minimize cycle risk
- Note no anticonvulsant except LTG until Stage 4
- Overlap and taper
- Follow ADA guidelines regarding metabolic monitoring

TIMA Bipolar 2005 Acute Depression

Stage 4

**Combinations (OFC combinations = 3 drugs)**

- Lamotrigine should not be combined with AD without antimanic
  - Includes VPA and CBZ at this point
- SSRI’s include CTP, FLX, PRX, SRT and FLV
- Some advocate the use of AD earlier but evidence is lacking
- Venlafaxine associated with more mania induction

BUP = bupropion; CBZ = carbamazepine; ECT = electroconvulsive therapy; Li = lithium; LTG = lamotrigine; OFC = olanzapine-fluoxetine combination; QTP = quetiapine; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine; VPA = valproate

Meta-Analysis of Antidepressant Trials

Response, N=662

Mendelowicz (1980) only 34/58 BP
Himmelhoch (1982) only 29/59 BP
Cohn (1989) FLX v. IMI v.PCB; 25% lithium
Tohen (2004) 456/662=72%, 100% OLZ

RR 1.86

Manic switching

RR 1.00 (CI .47-2.13)

Meta-Analysis of Antidepressant Switch

SSRI = placebo, TCA significantly higher

Unipolar
- Placebo, n=3788: 0.2%
- SSRI, n=10246: 0.5%
- TCA, n=2716: 0.7%

Bipolar
- Placebo, n=48: 4.20%
- SSRI, n=242: 3.70%
- TCA, n=125: 12.40%

Peet M. Br J Psychiatry 164:549, 1994
Antidepressant Switch Rates

12 studies, many including mood stabilizers

- Placebo, n=30: 3.0%
- SSRI, n=171: 4.1%
- TCA, n=177: 12.4%
- Bupropion, n=33: 21.2%
- Venlafaxine, n=30: 13.3%
- MAOI, n=106: 7.5%
- Li / VPA, n=16: 6.3%

Goldberg JF and Truman CJ. Bipolar Disorders 5:407, 2003
Depression After Euthymia or Mania

Prospective depressions, N=67, LCM avg 36.8 months

- Response to AD better after euthymia
  - 62.5% vs. 27.9%, (p<.05)

- AD response : switch ratio better
  - 10:1 vs .75-1

Durable Recovery by Treatment

Randomized Acute Depression


© M H Allen 2007
Remission by Bipolar Type

Depression Scores by Treatment

Open, Selective Treatment

**MS + AD numerical superiority with anxiety**

Standard Care, \( n = 960 \)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No MS, No AD N=91</th>
<th>AD Alone N=51</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Remission</td>
<td>34.1%</td>
<td>33.3%</td>
<td>.9294</td>
</tr>
<tr>
<td>Durable Recovery</td>
<td>23.1%</td>
<td>33.3%</td>
<td>.1854</td>
</tr>
<tr>
<td>Any Response</td>
<td>57.1%</td>
<td>66.7%</td>
<td>.2652</td>
</tr>
<tr>
<td>50% Improvement</td>
<td>25.3%</td>
<td>33.3%</td>
<td>.3057</td>
</tr>
<tr>
<td>Affective Switch</td>
<td>6.6%</td>
<td>9.8%</td>
<td>.4923</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MS Alone N=211</th>
<th>MS + AD N=509</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Remission</td>
<td>36.3%</td>
<td>38.4%</td>
<td>.5959</td>
</tr>
<tr>
<td>Durable Recovery</td>
<td>33.9%</td>
<td>36.0%</td>
<td>.5909</td>
</tr>
<tr>
<td>Any Response</td>
<td>70.2%</td>
<td>74.4%</td>
<td>.2574</td>
</tr>
<tr>
<td>50% Improvement</td>
<td>39.1%</td>
<td>36.5%</td>
<td>.5203</td>
</tr>
<tr>
<td>Affective Switch</td>
<td>13.0%</td>
<td>15.6%</td>
<td>.3533</td>
</tr>
</tbody>
</table>
Open Selective Antidepressant Treatment

- Much larger sample
- Mood stabilizer, MS + AD, AD only
- Numerical differences favor AD
- Anxiety predicted response
Lamotrigine

LTG 50 mg/day (n = 64)
LTG 200 mg/day (n = 63)
Placebo (n = 65)

LOCF = last-observation-carried-forward.

* P<0.1; † P<0.05. LOCF = last-observation-carried-forward.

Lamotrigine, Hamilton $\geq 24$

“Modest benefit”
- Overall NNT = 11
- Ham $\geq 24$, NNT = 7

Geddes J R et al. BJP 2009;194:4-9

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MADRS Difference from Baseline

Aripiprazole, p = .236
Lithium, p = .245
Olanzapine, p = .004
OFC, p = .000
  MADRS -6.6 vs placebo
Paroxetine, p = .554
MADRS Difference from Baseline

Quetiapine 300 mg, p=.000
MADRS -4.84 vs placebo

Quetiapine 600 mg, p=.000
MADRS -4.75 vs placebo

Divalproex Response vs Placebo

*Divalproex Monotherapy in Bipolar Depression*

- Depakote, 22/69 vs Placebo, 10/69, p=.02
- RR of response = 2.1

Quetiapine in Bipolar I and Bipolar II

Baseline values: aquetiapine XR, 30.2; placebo, 30.1; bquetiapine XR, 28.1; placebo, 30.3
MITT, MMRM, OC

Suppes et al 2010. *p<0.05; ***p<0.001 vs placebo

EMBOLDEN I and II; BOLDER I and II
ITT, LOCF

AstraZeneca Data on File. ‡p<0.001 vs. placebo.
Quetiapine and Rapid Cycling

**TRIAL 002**
Baseline values: aquetiapine XR, 29.5; placebo, 30.8; bquetiapine XR, 29.9; placebo, 30.0

MITT, MMRM, OC

Suppes et al 2010. **p<0.01; ***p<0.001 vs placebo

EMBOLDEN I and II; BOLDER I and II
Rapid cycling, ≥4 episodes in past year.
ITT, LOCF

AstraZeneca Data on File. ‡‡P<0.001 vs placebo.
Quetiapine Item Analysis

- Apparent sadness
- Reported sadness
- Inner tension
- Reduced sleep
- Reduced appetite
- Concentration difficulties
- Lassitude
- Inability to feel
- Pessimistic thoughts
- Suicidal thoughts

Mean % Change in Score

* $p < 0.05$  † $p < 0.01$  § $p < 0.001$ vs placebo

Quetiapine 600 mg (n=170)
Quetiapine 300 mg (n=172)
Placebo (n=169)
Summary Bipolar Depression

- **Antidepressants**
  - Little evidence favoring, some adverse

- **Olanzapine, olanzapine/fluoxetine**
  - 1 study, large effects

- **Lamotrigine**
  - 5 studies, “modest benefit”

- **Depakote**
  - Small numbers, doubled response rate

- **Lithium**
  - Mostly antimanic

- **Quetiapine**
  - 4 studies, array of symptoms, BP 1 and 2, RC
Maintenance Treatment
General Principles

Maintenance Phase

- Anticipated maintenance treatment influences acute treatment
  - Tendency to relapse to the same or opposite polarity?
  - Agents vary in prevention of different polarity
- Continue effective acute phase treatment(s)
- Switch to one with evidence of maintenance efficacy ??
  - “Maintenance” = enrichment, discontinuation
  - Discontinuation, even AD, is associated with relapse
- Improve tolerability and adherence
  - Little data on combinations in maintenance
Relapse to Mania Relative to Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lamotrigine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calabrese et al (26/165; 19/119)</td>
<td>0.75 (0.41, 1.35)</td>
<td>47.9</td>
</tr>
<tr>
<td>Bowden et al (20/58; 28/69)</td>
<td>0.73 (0.41, 1.29)</td>
<td>52.1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.74 (0.49, 1.11)</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calabrese et al (10/120; 19/119)</td>
<td>0.42 (0.19, 0.90)</td>
<td>28.1</td>
</tr>
<tr>
<td>Bowden et al (16/90; 17/92)</td>
<td>0.87 (0.44, 1.72)</td>
<td>35.3</td>
</tr>
<tr>
<td>Bowden et al (8/44; 28/69)</td>
<td>0.39 (0.20, 0.76)</td>
<td>36.7</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.53 (0.35, 0.79)</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Valproate semisodium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowden et al (27/187; 17/92)</td>
<td>0.73 (0.39, 1.36)</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.73 (0.39, 1.36)</td>
<td>100.0</td>
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Relapse to Depression Relative to Placebo

**Lamotrigine**
- Calabrese et al (57/166; 47/119)
- Bowden et al (8/58; 21/69)
  - Subtotal

**Lithium**
- Calabrese et al (47/120; 47/119)
- Bowden et al (10/44; 21/69)
  - Subtotal

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<tr>
<td>Calabrese et al (57/166; 47/119)</td>
<td>0.67 (0.46, 0.99)</td>
<td>77.9</td>
</tr>
<tr>
<td>Bowden et al (8/58; 21/69)</td>
<td>0.56 (0.27, 1.16)</td>
<td>22.1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>0.65 (0.46, 0.91)</strong></td>
<td><strong>100.0</strong></td>
</tr>
<tr>
<td>Calabrese et al (47/120; 47/119)</td>
<td>0.77 (0.51, 1.16)</td>
<td>75.9</td>
</tr>
<tr>
<td>Bowden et al (10/44; 21/69)</td>
<td>0.60 (0.29, 1.24)</td>
<td>24.1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>0.73 (0.51, 1.04)</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Lithium Meta-analysis

Five RCT’s, Li vs. placebo, n=770

- One relapse prevented for every 14 patients treated 1-2 years
  - One mania for every 10 patients
  - One depression for every 14 patients
- Better for manic than depressive relapse

Recurrence of Mania, Quetiapine vs. Lithium or Placebo

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP vs PLA</td>
<td>0.29</td>
<td>0.21, 0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTP vs LI</td>
<td>0.78</td>
<td>0.53, 1.16</td>
<td>NS</td>
</tr>
<tr>
<td>LI vs PLA</td>
<td>0.37</td>
<td>0.27, 0.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Study 144, ITT population
Nolen et al 2009
Recurrence of Depression
Quetiapine vs. Lithium or Placebo

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<th>HR</th>
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<td>0.59</td>
<td>0.42, 0.84</td>
<td>&lt;0.01</td>
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</tbody>
</table>

Study 144, ITT population
Nolen et al 2009
Psychotherapy
Psychotherapy Interventions

Therapies may use some or all

- Adjust to Dx and Rx
- Enhance adherence
- Improve self-esteem
- Reduce risky behaviors
- Modify destabilizing biospsychosocial factors
- Manage stressors
- Teach coping strategies
- Teach early recognition
- Modify attitudes/beliefs
- Homework

Scott J and Gutierrez MJ. Bipolar Disorders 2004; 6:498
Evidence Based Therapies

*Impact relapse and rehospitalization rates*

- **Group psychoeducation**
  - 25% hospitalized vs 35% in unstructured group

- **Cognitive behavioral therapy (CBT)**
  - 1 year relapse 44% vs 75% usual care

- **Family focused therapy (FFT)**
  - 2 year relapse 28% vs 60% supportive
  - Perceived criticism may be an indicator

- **Interpersonal social rhythm therapy (IPSRT)**
  - Trend to earlier recovery, no effect on relapse

---

**Psychotherapy Improves Relapse Rate**

*Effect size in large RCT's = .37*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Effect on</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colom, et al, 2003</td>
<td>120</td>
<td>.41</td>
<td>.02</td>
</tr>
<tr>
<td>Lam, et al, 2003</td>
<td>96</td>
<td>.26</td>
<td>.00</td>
</tr>
<tr>
<td>Miklowitz, et al, 2000</td>
<td>101</td>
<td>.46</td>
<td>.08</td>
</tr>
<tr>
<td>Fixed (3)</td>
<td>317</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>Random (3)</td>
<td>317</td>
<td>.37</td>
<td></td>
</tr>
</tbody>
</table>

Scott J and Gutierrez MJ. Bipolar Disorders 2004; 6:498
Interpersonal & Social Rhythm Therapy (IPSRT)

- Stabilize daily routines and sleep/wake cycles
- Gain insight into the bi-directional relationship between moods and interpersonal events
- Ameliorate interpersonal problems related to grief, role transitions, role disputes, interpersonal deficits

Interpersonal Social Rhythm Therapy

\textit{RCT, IPSRT vs ICM, n=175 BP1, 2 years}

- Effect size of \(0.58\)
  - after controlling marital status, index polarity, anxiety, medical burden

- Mediated by improved social rhythms
  - Not adherence
  - Better if married

- Best initiated in early maintenance

- ICM better if medically ill and anxious

Frank E, et al. Arch Gen Psychiatry 2005; 62:996
Integrated Family & Individual Therapy (IFIT) Increases Time in Remission


\[ \chi^2 (1) = 5.63, P = <.02. \]
Family-Focused Treatment (FFT) of Bipolar Disorder

- 21 outpatient sessions over 9 months
- Assessment of patient and family
- Psychoeducation about bipolar disorder
  - symptoms, early recognition, etiology, treatment, self-management
- Communication enhancement training
  - rehearsal of effective speaking and listening strategies
- Problem-solving skills training

FFT + Meds Delays Relapse More Than Crisis Management + Meds

CM vs. FFT $\chi^2 (1) = 8.71, p = .003$; FFT, mean survival = 73.5 weeks; CM, 53.2 weeks.
Miklowitz DJ, et al. *Arch Gen Psychiatry*. 2003
FFT Delays Rehospitalization vs Individual

UCLA FFT Study (N=53)

\[ X^2 (1) = 3.87, P < .05 \]


*Family-focused treatment*

*Individually-focused treatment*
CBT for Bipolar

- Psychoeducation: a diathesis-stress model
- Cognitive behavioral skills: to monitor mood and prodromes; to modify behavior
- Importance of routine and sleep
- Dealing with long-term vulnerability issues: e.g., dysfunctional high goal-attainment beliefs

Lam DH, et al. *Arch Gen Psychiatry.* 2003;60:145-152.
Hazard ratio for relapse = 0.40, P = .004, controlling for med. compliance.