Long Term Stabilization of Bipolar Disorder: Integrating the old with the new

Frederick K Goodwin MD
Director, Psychopharmacology Research Center
George Washington University Medical Center
Washington DC

Former Director, NIMH
Is Bipolar disorder over-diagnosed or under-diagnosed or both?

There are indications that in some settings some axis II patients are being diagnosed as bipolar; often this is diagnostic inflation for insurance purposes.

On the other hand, there are 5 studies of Bipolar I patients indicating that for each one properly diagnosed there is one improperly diagnosed as unipolar depression – i.e. 50% under-diagnosis
Underdiagnosis of Bipolar Disorder

- Iowa 500 study
- Sample A: Personal interview only
- Sample B: Personal interview and/or hospital chart

Morbidity risk for mania in first-degree probands

<table>
<thead>
<tr>
<th></th>
<th>SZ</th>
<th>Mania</th>
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<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>2</td>
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<tr>
<td>B</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Under-diagnosis of Bipolar Depression: The NIMH experience

• Patients admitted with major depression
  – Screened for bipolar disorder by 2 separate 1 hr psychiatric interviews
  – Family member interviewed by another investigator interested in genetics
  – Input from the family resulted in twice as many bipolar I diagnoses as the patient interviews had

Gershon et al 1988
Unipolar Misdiagnosis May Lead to Inappropriate Treatment

Percent of misdiagnosed bipolar patients who developed mania/hypomania or rapid cycling while taking antidepressants

- Naturalistic study done with chart review of 85 patients
- Bipolar depression misdiagnosed as unipolar in **56%** of patients
- Antidepressants used earlier and more often than mood stabilizers

How long does diagnosis take?


UP vs. BP, t=-2.8, p=0.007; Differences between BP subtypes, F=2., p=0.09
High Bipolarity Risk in Prepubertal and Severe Adolescent / Young Adult Major Depression

Prepubertal Major Depression
(Age at intake 10.3 yrs)
49% Bipolar at 10-year follow-up

- 33.3% (24/72) BPI
- 15.3% (11/72) BPII
- 51.4% (37/72) Not BP

Adolescents / Young Adults
Hospitalized for Major Depression
(Age at intake 23.0 yrs)
41% Bipolar at 15-year follow-up

- 14.8% (11/74) BPI
- 59.4% (44/74) BPII
- 25.6% (19/74) Not BP

Contributions to the misdiagnosis of BP Depression as Unipolar

• Failure to involve a family member in the evaluation of depressed patients
• DSM IV, by initially separating out Bipolar from all depressive disorders, obscures the close relationship between Bipolar and the early onset, recurrent forms of unipolar depression
DSM-IV Classification of Mood Disorders

Mood disorders

Bipolar disorders
- Bipolar I disorder
- Bipolar II disorder
- Cyclothymic disorder
- Bipolar disorder NOS

Depressive disorders
- Major depressive disorder
- Dysthymic disorder
- Depressive disorder NOS
- Single episode
- Recurrent
Highly Recurrent Unipolar Depression (Cyclic Depression)

- Bipolar FH
- Bipolar-like age of onset (teens and 20s)
- High episode frequency
- Manic/hypomaniac switch with Antidepressants
- Prophylaxis with Lithium > Imipramine
  - (Lithium is anti-cyclic not just anti-bipolar)
- Prophylaxis with Lamotrigine?
- DSM IV HAS NO SUCH CATEGORY
% Patients Relapsing (< 1 YR)

Unipolar

- Lithium: 22%
- Tri-Cyclics: 65%
- Placebo: 67%

Bipolar

- Lithium: 20%
- Tri-Cyclics: 59%
- Placebo: 68%

Legend:
- Orange: Medication
- Cyan: Placebo
Kraepelin’s Manic-Depressive Illness
Mood or Affective Disorders

**Recurrent (Episodic)**
- > 3 Episodes; Onset < age 30
  (Kraepelin’s Manic-Depressive Illness)
  - **Bipolar**
    - BPI
    - BP N.O.S.
    - Cyclothymia
  - **Unipolar**
    - Psychotic
    - Non-Psychotic

**Depressive Disorders**
- < 3 Episodes; Onset < age 30
  - Major Depression
  - Dysthmia
  - Depressive Disorder N.O.S.
  - Psychotic
  - Non-Psychotic

“The Bipolar Spectrum”
Clues to a potential Bipolar or cyclic diathesis

1. Recurrent major depressive episodes (> 3)
2. Early age of onset of major depressive episode (< 25)
3. Family history of bipolar disorder in first-degree relative
4. Hyperthymic personality (prior to depression)
5. Atypical depressive symptoms (DSM-IV criteria)
6. Brief major depressive episodes (average < 3 months)
7. Psychotic major depressive episodes
8. Postpartum depression
9. Antidepressant-induced mania or hypomania
10. Antidepressant “wear-off”
11. Lack of response to 3 adequate antidepressant trials
12. TO EVALUATE THESE, IT IS CRITICAL TO INCLUDE A FAMILY MEMBER AND USE A LIFE CHART

Goodwin and Ghaemi 2004
Management of Bipolar Disorder

- Monitor course with life chart
- Recognize and treat substance abuse
- Treat side-effects vigorously
- Psychotherapy: Focus on compliance, psychoeducation and circadian integrity
- Often requires several medications
- Depression is 2/3rds of the morbidity and yet antidepressants may induce mania and/or cycling
- High suicide risk

Depression is 2/3rds of Bipolar morbidity

How well do mood stabilizers protect against recurrence of depressive episodes?
Three Phases of Drug Treatment of Affective Disorders

- Acute
- Continuation
- Maintenance or prophylaxis: i.e. mood stabilizer

- Control of acute symptoms
- Maintain control of acute episode
- Prevent or attenuate new episodes

Goodwin, Jamison 1990
Summary of Double-Blind Lithium vs Placebo Maintenance Trials in 1970s

Lithium Compared to Placebo, Primarily After Manic/Mixed Episodes

- **Superior Episode Prevention**
  - Lithium (n=251): 81%
  - Placebo (n=263): 56%

- **Superior Depression Prevention**
  - Lithium (n=251): 34%
  - Placebo (n=263): 21%

- **Superior Mania Prevention**
  - Lithium (n=251): 37%
  - Placebo (n=263): 23%

Risk ratios of events relative to patients on Li (controlling for comorbid Dx & coexisting meds)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Outpatient attempts</th>
<th>Inpatient attempts</th>
<th>Completed suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Divalproex</td>
<td>1.7***</td>
<td>1.6***</td>
<td>2.6**</td>
</tr>
</tbody>
</table>

**P < .01, ***P < .001.

Divalproex in Maintenance Treatment

- In the randomized placebo controlled trial neither divalproex nor lithium separated from placebo on the primary outcome.

- Open data indicate that prophylactic antimanic effect is greater than antidepressant effect.

- Secondary analysis of randomized study: Rescue antidepressants needed: Divalproex < Placebo (p<.01)

Relapse defined by Hospitalization and/or YMRS ≥15 and/or HAM-D ≥15.

Time to relapse into mania or depression with olanzapine versus placebo

Aripiprazole Compared to Placebo After Manic/Mixed Episodes responded acutely to it

Stabilized on ARI before randomization.
Study Design
Currently or Recently Manic/Hypomaniac Patients

Screen

Open Label
Lamotrigine 100-200 mg/day

Concomitant psychotropics

Stable pts randomized

Double-Blind Time to Intervention

Lamotrigine 100-400 mg/day (n=59)

Lithium 0.8-1.1 mEq/L (n=46)

Placebo (n=70)

2 weeks

8-16 weeks

76 weeks

Bipolar I currently or recently manic/hypomaniac

Combined Analysis of the 2 Trials

- **Time to intervention for any episode**
  - Both lithium and lamotrigine > placebo
  - Lithium = lamotrigine (p=0.625)

- **Time to intervention for Mania**
  - Both lithium and lamotrigine > placebo
  - Lithium > lamotrigine

- **Time to intervention for Depression**
  - Lamotrigine > placebo
  - Lithium vs. placebo n.s. trend (p=0.12)
  - Lamotrigine vs. lithium n.s. (p=0.325)

Goodwin et al. 2004
Both Lithium and Lamotrigine prevent Mania more effectively than Placebo

Estimated % of pts intervention-free*

- Lamotrigine 100-400 mg (n=223)
- Lithium (n=164)
- Placebo (n=188)

Month

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Percent of patients

18 mo

65 80 53

LTG vs PBO, $P=0.034$
Li vs PBO, $P=0.001$
LTG vs Li, $P=0.030$

* Some patients considered intervention-free for manic episodes could have had intervention for depressive episodes.

Data on file, GlaxoSmithKline.
Lamotrigine and lithium reduce recurrences not just relapses

• Analysis of the two 18 month trials showed that both drugs continue to robustly separate from placebo during the period from 6 to 18 months.
• Lithium and lamotrigine are thus the only drugs that have been shown to prevent new episodes; that is they are the only drugs that qualify as mood stabilizers, when that term is properly defined
• Also, analysis of the 18 mo placebo data indicated that, 85% of the time, the next new episode was of opposite polarity
Incidence of Mania/Hypomania/Mixed Episodes
Combined Analysis

Percent of patients

- Lamotrigine (n=227)
- Lithium (n=166)
- Placebo (n=190)
We’ve reviewed data on prevention of depression. What about the acute treatment of bipolar depression?
## Initial Prescriptions for 7760 US Bipolar Disorder Patients

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>49.8</td>
</tr>
<tr>
<td>Modern</td>
<td>47.4</td>
</tr>
<tr>
<td>Older (TCAs, MAOIs)</td>
<td>2.42</td>
</tr>
<tr>
<td><strong>Mood-stabilizers</strong></td>
<td>24.6</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>8.31</td>
</tr>
<tr>
<td>Other anticonvulsants</td>
<td>8.84</td>
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<tr>
<td>Lithium salts</td>
<td>7.49</td>
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<tr>
<td><strong>Sedative-anxiolytics</strong></td>
<td>14.8</td>
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<tr>
<td><strong>Antipsychotics</strong></td>
<td>10.7</td>
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<tr>
<td>Modern agents</td>
<td>10.1</td>
</tr>
<tr>
<td>Older neuroleptics</td>
<td>0.58</td>
</tr>
</tbody>
</table>

• Risk-benefit ratio of antidepressants:
  – the risks
Frequency of Risks associated with antidepressants in Bipolar Disorder

• Acute Switch (within 2 mo of starting AD)
  – TCAs=MAOIs - 30-60%
  – SRIs, Bupropion, Venlafaxine - 20%
  – Switch rates generally lower in the presence of a Mood stabilizer

  Ghaemi and Goodwin 04

• Destabilization (2 more episodes than before)
  – TCAs=SRIs - 10% of trials, 25% of the patients
  – Mood stabilizers appear unprotective
  – Difficult to detect without a life chart

  Ghaemi et al 04
The Antidepressant Problem

- 3 year prospective maintenance f/u
- n=75 randomized DB
- Li vs. Li+IMI
- 13 manic relapses
- Ave. relapse time 7-19 months, so it was destabilization, not acute switch
Time to Relapse Among Subjects With Bipolar Disorder Who Discontinued Antidepressant Treatment

Proportion of Subjects Not Relapsing

Number of Weeks Until Relapse

p=.006 <6 vs >12

A Randomized Study of Long-term AD Outcome in BP

- Open Randomization Study Begins
- Acute Bipolar Depression Responded to a Mood stabilizer (MS) and Antidepressant (AD) (2 months)
- Continue Mood stabilizer and Antidepressant
- Taper & Discontinue Antidepressant Continue Mood stabilizer alone
- 1 year n=40 per arm

SN Ghaemi, DJ Hsu, T Pardo, FK Goodwin, RJ Baldessarini, 2004, Abstract, APA annual meeting, New York
Randomized 1 yr comparison of MS alone vs MS + AD

• 24 % more episodes in the MS+AD group

• Among the rapid cyclers, the MS+AD group had more than twice as many episodes, principally depressive episodes
• WHAT ABOUT ANTIDEPRESSANT EFFICACY IN BIPOLAR DEPRESSION?
Outcomes

Response and remission use IDS criterion only;
Manic switch and Remission/no switch use YMRS or CGI BP

RM Post et al, Archives of Gen Psychiatry, in press
Conclusions

I. Brief hypomanias are common, as are full switches (hypomania, mania)
   ♦ In acute trials (10 weeks), 19.3% showed full switches on ADs
   ♦ In continuation (≤ 1 year), 36.7% showed full switches on ADs

II. Venlafaxine had a higher ratio (3.76) of full switches (hM + M) to brief hypomanias (BH + RBH) compared to bupropion .95 and sertraline (1.67), suggesting the highest risk for progression to more severe/sustained hypomanias on venlafaxine.

III. In continuation, the small number of Rapid Cyclers showed the lowest switch rate on bupropion (16.7%) and the highest on venlafaxine (62.5%).

IV. Thus, of the original 228 adjunctive AD trials in these bipolar outpatients, only 16.2% (37/228) were associated with a sustained long-term AD response in continuation without a switch.
Antidepressants in Bipolar Depression: The Texas Algorithm

• (1) If on lithium increase level to >0.8; add lamotrigine; if not on antimanic, start lamotrigine (with antimanic if BP I)
• (2) Quetiapine or OFC
• (3) Combination (Li + ltg; li or ltg + QTP or OFC)
• (4) Combination of 1 or 2 of the above (or CBZ or VPA) with antidepressant
• (5) Adjunctive MAOI, TCA, pramipexol, thyroid
AD’s in Bipolar: Conclusions

- Maintenance antidepressants efficacy is not established in Bipolar Disorder
- Switches and/or cycling on antidepressants demonstrated in 3 randomized Pb contr studies
- Antidepressant monotherapy is contraindicated in bipolar I disorder; Bipolar II?
- Antidepressants (with a Mood Stabilizer) should generally be reserved for severe BP depression, or when adjunctive Mood Stabilizers have failed
- When antidepressants are used, taper and discontinue them after recovery from depression; maintain them only in those who repeatedly relapse soon after discontinuation (about 20% of bipolar pts)

SN Ghaemi, DJ Hsu, F Soldani, FK Goodwin, Bipolar Disorders, December 2003, 5: 421-433
If antidepressants have an equivocal risk-benefit ratio in bipolar I depression, what about mood stabilizers themselves as acute antidepressant agents?
Controlled Trials of Mood Stabilizers for the Acute Treatment of Bipolar Depression

- Lithium: 9 studies; small to moderate effects
- Divalproex: 1 study; relatively small effect
- Olanzapine: 1 study; small effect
- Lamotrigine: 3 studies; moderate to robust effects; 2 failed studies with high placebo response rates
- Quetiapine: 2 studies; moderate to robust effects, but prophylaxis not yet established
### Major drawbacks to existing mood stabilizers

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<th>Weight Gain</th>
<th>Lithium</th>
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<tbody>
<tr>
<td></td>
<td>Divalproex</td>
<td>++</td>
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<tr>
<td></td>
<td>Lamotrigine</td>
<td>-</td>
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<tr>
<td></td>
<td>Olanzapine</td>
<td>+++</td>
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<tr>
<td>Neurocognitive SE</td>
<td>Lithium</td>
<td>++</td>
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<tr>
<td></td>
<td>Divalproex</td>
<td>+ or ++</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>-?</td>
</tr>
<tr>
<td>Prevention of depression</td>
<td>Lithium</td>
<td>+</td>
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<tr>
<td></td>
<td>Divalproex</td>
<td>+ ?</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>+</td>
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Goodwin 2004
What are the most important developments in BP Rx since the 1st edition of Goodwin and Jamison’s Manic Depressive Illness (1990)

- The development of the first highly tolerable maintenance treatment to stabilize effectively from below without triggering mania – Lamotrigine
- Psychiatry’s first demonstration that we have a treatment that can save lives – Lithium
- The development of atypical antipsychotics (a class whose potential as MSs is not yet known)
- The development of the new antimanic ACs (replicating Carbemazepine, stabilizing primarily from above (Depakote, Trileptal ?))
THE END
Questions?
Comments?
Differential Diagnosis of Early-Onset Bipolar Disorder and ADHD

True euphoria, decreased need for sleep and hypersexuality are uncommon in attention-deficit hyperactivity disorder (ADHD) but common in bipolar disorder.

- Onset of symptoms including inattention typically >7 years of age in bipolar disorder but earlier in ADHD.

- Family history of bipolar disorder more common in those with bipolar disorder, whereas disruptive disorders such as conduct disorder are more common in those with ADHD.

- Periods of normal function may be seen in those with bipolar disorder but rare in those with ADHD.
Presentation of Mania in Pediatric Patients with Bipolar Disorder

Erratic, not persistent, changes in mood, level of psychomotor agitation, and mental excitement

Irritability, belligerence, and mixed state features more common than euphoria

Reckless behaviors: school failure, fighting, dangerous play, inappropriate sexualized activity

Psychotic symptoms, mood-incongruent hallucinations, paranoia, market thought disorder

Severe deterioration in behavior