Antidepressants in Bipolar Depression: An Update

S. Nassir Ghaemi, MD, MPH
Professor of Psychiatry, Tufts University School of Medicine
Director, Mood Disorders Program, Tufts Medical Center
Lecturer, Harvard Medical School
Boston, Massachusetts

Introduction

- Antidepressants are the most commonly used class of medications in bipolar illness
- None are FDA indicated for acute bipolar depression
- None are FDA indicated for prevention of bipolar depression
- Risks of mania and rapid cycling have been raised
- Expert guidelines do NOT recommend them as first-line treatment in bipolar depression
- The research evidence is much more limited than in MDD

MDD = major depressive disorder.
Antidepressant-Induced Mania: TCAs

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.


Stanley Network: RCT of New Antidepressants in Bipolar Depression up to 1 Year

• Predictors:
  – BD-I (12%) > BD-II (2%)
  – Rapid cycling?
• Only in venlafaxine after 2 months: ie, long-term destabilization: 61% in rapid cyclers vs 39% in non-rapid cyclers

N = 228.

Antidepressant-Related Mania is Diagnostic of Bipolar Illness

• STAR*D: Manic switch rate: 2/4041 = 0.05%
• STEP-BD: 366 randomized patients = 10%
• Relative Risk: 204.3 [95% CIs: 49.4, 844.1]

STAR*D = Sequenced Treatment Alternatives to Relieve Depression.


Antidepressant-Related Mania is Diagnostic of Bipolar Illness

• Mood Destabilization Defined
  • Acute manic switch = antidepressant-induced mania
    – Up to 2 months
  • Long-term mood destabilization
    – > 2 months
    • Cycle acceleration
      – At least ≥ 2 mood episodes in a period treated with ADs vs similar periods without ADs
    • Rapid cycling
      – De novo or exacerbation
      – May represent depression > mania

AD = antidepressant.


A Priori Subgroup Analysis: Rapid Cycling

• Excess of depressive recurrences/year was limited to AD-treated patients
  – Rapid cycling = 1.29 vs non-rapid cycling = 0.42 major depressive episodes in the first year, a 3.1-fold excess; z = −2.04, P = .04
  – Not the AD-discontinued group (rapid cycling = 0.82 vs non-rapid cycling = 0.70 episodes/year, only a 1.17-fold difference)


First Randomized Discontinuation Study with New Antidepressants in Bipolar Disorder

Open Randomization Study begins

Acute Bipolar Depression Responded to a MS + AD
(2 months)

Continue MS + AD

Discontinue AD
Continue MS Alone

1 Year
N = 40
Per Arm

MS = mood stabilizer.

Treatment Refractory Bipolar Disorder

- Therapeutic mood stabilizer trial
  - Dose: lithium = 0.8 ng/dL, valproate ≥ 70 ng/dL, carbamazepine ≥ 6 ng/dL, lamotrigine ≥ 100 mg/day
  - Duration: 2 cycles of the natural history
  - In the absence of ADs
- ADs are mood destabilizers
  - Counteract the benefits of mood stabilizers
- My hypothesis: 50% of treatment-resistant BD resolve by discontinuation of ADs
  - Like treatment-resistant depression: 50% resolve by addition of mood stabilizers


Citalopram in Bipolar Depression: A Double-Blind, Placebo Controlled Acute and Maintenance Study

- n = 124
- Acute phase 6 weeks
- Maintenance 1 year

ClinicalTrials.gov Identifier: NCT00562861.

Citalopram in Bipolar Depression: A Double-Blind, Placebo Controlled Acute and Maintenance Study (continued)

BD-II: Antidepressant-Induced Mania

- Meta-Analysis from Clinical Trials
  - Unipolar Depression
  - Bipolar Depression
  - Switching to Mania (%)

SSRI = fluoxetine, fluvoxamine, paroxetine, or sertraline.

BD-II RCT: Fluoxetine vs Lithium

- Relapse Prevention
  - “Enriched” preselects fluoxetine responders
  - Does not preselect lithium responders
  - 24.3% of initial sample (n = 148) had manic symptoms with fluoxetine

STEP-BD Antidepressant Discontinuation RCT: BD-I vs BD-II

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antidepressant Continued</th>
<th>Antidepressant Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Exposure (weeks)</td>
<td>94.2 [91.4 to 97.2]</td>
<td>83.8 [80.0 to 90.0]</td>
</tr>
<tr>
<td>Response/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.76 ± 0.50</td>
<td>0.50 ± 0.27</td>
</tr>
<tr>
<td>Manic/Hypomania</td>
<td>0.15 ± 0.45</td>
<td>0.35 ± 0.30</td>
</tr>
<tr>
<td>Total</td>
<td>0.91 ± 1.06</td>
<td>0.86 ± 0.37</td>
</tr>
<tr>
<td>% Weeks no episodes</td>
<td>74.7 [70.0 to 80.4]</td>
<td>75.0 [66.2 to 83.4]</td>
</tr>
</tbody>
</table>


Bipolar “Depression”

- What is the psychopathology of “depression”?

Mixed Depression

Koukopoulos’ Criteria

- Major depression + 3 of 9 criteria
  - Mood lability
  - Marked irritability
  - Absence of psychomotor retardation
  - Flight of ideas
  - Increased libido
  - High blood pressure
  - Marked anxiety
  - Marked insomnia
  - Sexual impulsivity


BRIDGE Study

- N = 5635 with clinical depression
- DSM-IV criteria for BD = 16.0%
- Bipolarity specifier = 47.0%
  - ≥ 3 manic symptoms
  - No duration criterion
  - Marked impairment of functioning or unequivocal and observable change from usual behavior
- Bipolarity specifier highly associated with AD-induced mania (OR = 9.5) and family history of BD (OR = 3.8)

BRIDGE = Bipolar Disorders: Improving Diagnosis, Guidance and Education.
International Mood Network: Validation of Koukopoulos’ Criteria for Mixed Depression

- N = 435 (10 countries), age 39 ± 14 years, 61% female, 51% BD-I, 21% MDD, 26% BD-II/NOS
- 9% met DSM-IV mixed criteria
- 51% met Koukopoulos criteria for MdD
- Clinically differential features of MdD vs pure depression
  - 7.9× more past trauma
  - 23% more depressive episodes
  - 55% fewer hospitalizations


Low Antidepressant Response in Mixed Depression

- 9% met DSM-IV mixed criteria
- 51% met Koukopoulos criteria for MdD
- Clinically differential features of MdD vs pure depression
  - 7.9× more past trauma
  - 23% more depressive episodes
  - 55% fewer hospitalizations


Mixed Depression (Koukopoulos’ Criteria): Rome Study

- N = 219, Rome
  - Using DSM-IV: 12% BD-I, 20.5% BD-II, 46% MDD
  - Age: 45 years, 11% rapid-cycling
  - Temperament
    - 63% hyperthymic, 13% cyclothymic, 7% dysthymic
    - 10% normal
  - 51% AD-induced mixed depression
    - More in BD-II than MDD, 45% TCAs, 38% SSRIs
    - Suicide attempts: 2.5× more than non-AD MdD


Rome Study: Follow-up 1.3 years

- 31.5% mood stabilizers, 30% dopamine blockers, 25% ECT
- ONLY 2.7% given antidepressants
- HAM-D: 27.9 to 8.0
- Episodes: 45% NONE, 19% minor depressive, 17% pure depressive, 8% hypomanic, 7% mixed depressive, 1% suicide attempt

ECT = electroconvulsive therapy; HAM-D = Hamilton Rating Scale for Depression.

Conclusions

- The research evidence does NOT support efficacy of antidepressants with any appreciable clinical benefit in acute bipolar depression
- The research evidence does NOT support efficacy of antidepressants with any appreciable clinical benefit in prevention of bipolar depression
- Evidence of acute manic switch exists but is limited with newer agents
- Evidence of long-term worsening of bipolar illness exists especially in rapid-cycling patients

Practical Take-Aways

- Antidepressants have little to no benefit in acute or maintenance treatment of bipolar depression, and thus should not be used in most patients
- Antidepressants cause more mood episodes over time in patients with rapid cycling bipolar illness, and thus should be stopped
- In refractory bipolar illness, antidepressants have mood destabilizing effects and counteract benefits of mood stabilizers, and thus should be stopped