The Pharmacological Management of Bipolar Disorder: An Update

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Declaration of Interests

• I have received:
  ▪ Speaker fees from:
    • Astra Zeneca, BMS, Eli Lilly, GSK, Janssen-Cilag, Lundbeck, Organon, Pfizer, Wyeth
  ▪ Consultancy fees from:
    • Astra Zeneca, BMS, Cyberonics, Eli Lilly, Janssen-Cilag, Lundbeck, Servier, Wyeth
  ▪ Independent investigator led research support from:
    • Astra Zeneca, Eli Lilly and Wyeth
Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care
A Spectrum of Affective Disorders

Normal fluctuation
Unipolar Depression
Bipolar II
Bipolar I

Mania
Depression
Mania
Valproate and Lithium in acute mania
Bowden et al 1994

PERCENTAGE WITH MARKED (>50%) IMPROVEMENT IN MRS SCORE

N.B. Efficacy of Depakote independent to prior responsiveness to Lithium
Compared to placebo, olanzapine patients had a statistically significantly greater LOCF mean improvement at week 1 which was maintained throughout the study.
**Quetiapine: Mania, acute treatment**

Change from baseline (YMRS)

- **Placebo (n=195)**
- **Quetiapine (n=208)**

Study 104 + 105

*\( p<0.05 \); **\( p<0.01 \); ***\( p<0.001 \)

Brecher & Huizar 2003; Paulsson & Huizar 2003; Jones & Huizar 2003
Risperidone in acute treatment of mania

LOCF analysis; *P<0.001 risperidone vs placebo;

Median dose 4mg/day
BL: Risperidone = 29.1; placebo = 29.2

Change in total YMRS score

Risperidone (n=134) Placebo (n=125)
Fig. 2 Mean change (s.e.) from baseline in Young Mania Rating Scale (YMRS) Total score, efficacy sample (last observation carried forward).a a. Baseline YMRS scores: placebo, 28.8; haloperidol, 28.0; aripiprazole, 28.4. *P<=0.05; **P<=0.01 v. placebo.
# Cotherapy vs monotherapy in mania

## RESPONSE

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical antipsychotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tohen, 2002b (149/220 51/114)</td>
<td>1.51 (1.21, 1.89)</td>
<td>51.0</td>
</tr>
<tr>
<td>Sachs, 2004 (44/81 29/89)</td>
<td>1.67 (1.16, 2.39)</td>
<td>21.0</td>
</tr>
<tr>
<td>DelBello, 2002 (13/15 8/15)</td>
<td>1.63 (0.97, 2.72)</td>
<td>6.1</td>
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<tr>
<td>Yatham, 2003 (40/68 30/73)</td>
<td>1.43 (1.02, 2.01)</td>
<td>22.0</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.53 (1.31, 1.80)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

- **Favours cotherapy**
- **Favours monotherapy**
Acute Mania:
Those not on anti-manic treatment

- Atypical antipsychotic (olanzapine, risperidone, quetiapine) for those with severe mania
  - If ineffective consider adding Li or valproate
- Valproate or Li if previous good response and compliance
  - Avoid valproate in women of child bearing potential
  - Li only if less severe
- Don’t use carbamazepine routinely and avoid gabapentine, lamotrigine and topiramte
Figure 1. Algorithm for Treatment of Acute Hypomanic/Manic/Mixed Episodes in Patients With Bipolar I Disorder

Stage 1
- Euphoric:
  - 1A: Li, VPA, ARP, QTP, RIS, ZIP
  - 1B: OLZ or CBZ
  - Nonresponse: Try Alternate Monotherapy
- Mixed:
  - 1A: VPA, ARP, RIS, ZIP
  - 1B: OLZ or CBZ
  - Nonresponse: Try Alternate Monotherapy

Stage 2
- Monotherapy
  - Li, VPA, AAP
  - Choose 2 (not 2 AAPs, not ARP or CLOZ)

Stage 3
- Two-Drug Combination
  - Li, VPA, AAPs, CBZ, OXC, TAP
  - Choose 2 (not 2 AAPs, not CLOZ)

Stage 4
- ECT or Add CLOZ or Li + [VPA or CBZ or OXC] + AAP

CONT
Depression
Depression is **THE** Problem

**Bipolar I**
(Judd et al. *Archives of General Psychiatry* 59:530-537, 2002)

- Symptomatic: 47%
- Asymptomatic: 53%
- Depressed: 67%
- Manic/hypomanic: 20%
- Mixed: 13%

**Bipolar II**
(Judd LL et al. *Archives of General Psychiatry* 60:261-269, 2003)

- Asymptomatic: 46%
- Symptomatic: 54%
- Depressed: 94%
- Hypomanic: 2%
- Mixed: 4%
Pharmacological treatments for bipolar depression

- Antidepressants
- Lithium
- Valproate
- Lamotrigine
- Antipsychotics
# Response in RCTs of Antidepressants vs Placebo in Bipolar Depression

<table>
<thead>
<tr>
<th>Study/ Subcategory</th>
<th>Antidepressant N of Subgroup/ Total N</th>
<th>Placebo N of Subgroup/ Total N</th>
<th>Risk Ratio (fixed) ±95% CI</th>
<th>Weight (%)</th>
<th>Risk Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Himmelhoch et al. 1982 (32)</td>
<td>20/28</td>
<td>4/31</td>
<td>5.30 5.54 2.15–14.23</td>
<td>9.41</td>
<td>2.90</td>
<td>1.26–6.69</td>
</tr>
<tr>
<td>Cohn et al. 1989 (31)</td>
<td>30/60</td>
<td>5/29</td>
<td>9.41 2.90 1.26–6.69</td>
<td>5.30</td>
<td>5.54</td>
<td>2.15–14.23</td>
</tr>
<tr>
<td>Tohen et al. 2004 (29)</td>
<td>46/86</td>
<td>137/370</td>
<td>72.14 1.44 1.14–1.83</td>
<td>5.30</td>
<td>5.54</td>
<td>2.15–14.23</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- **Total events**: 213 449
- **Total events**: 123 153

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Step BD study
Sachs et al. NEJM April, 2007

- 68% BPI, 32% BPII
- Antidepressants
  - n = 86 bupropion (300 mg/day)
  - n = 93 paroxetine (30 mg/day)
  - N = 187 placebo

\( p = 0.40 \)

\[ \text{Recovery} \]

\[ \text{MS + AD} \]

\[ \text{MS + plac} \]
## Manic Switch Rates in RCTs of Antidepressants vs Placebo

<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant</th>
<th>Placebo</th>
<th>Risk Ratio (Fixed) ±95% CI</th>
<th>Weight (%)</th>
<th>Risk Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendlewicz et al. 1980</td>
<td>0/39</td>
<td>0/19</td>
<td>Not estimable</td>
<td></td>
<td>Not estimable</td>
<td></td>
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<td>33</td>
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<td>Himmelhoch et al. 1982</td>
<td>0/28</td>
<td>0/31</td>
<td>Not estimable</td>
<td></td>
<td>Not estimable</td>
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<tr>
<td>32</td>
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</tr>
<tr>
<td>Cohn et al. 1989</td>
<td>2/60</td>
<td>1/29</td>
<td>10.95 0.97 0.09–10.23</td>
<td>10.95</td>
<td>0.97</td>
<td>0.09–10.23</td>
</tr>
<tr>
<td>31</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nemeroff et al. 2001</td>
<td>4/74</td>
<td>3/43</td>
<td>30.83 0.77 0.18–3.30</td>
<td>30.83</td>
<td>0.77</td>
<td>0.18–3.30</td>
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<tr>
<td>30</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tohen et al. 2004</td>
<td>5/86</td>
<td>19/370</td>
<td>58.22 1.13 0.43–2.95</td>
<td>58.22</td>
<td>1.13</td>
<td>0.43–2.95</td>
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<tr>
<td>29</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Total</td>
<td>287</td>
<td>492</td>
<td>100.00 1.00 0.47–2.13</td>
<td>100.00</td>
<td>1.00</td>
<td>0.47–2.13</td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Step BD study
Sachs et al. NEJM April, 2007

- 68% BPI, 32% BPII
- Antidepressants
  - n = 86 bupropion (300 mg/day)
  - n = 93 paroxetine (30 mg/day)
- N = 187
Antidepressant-Induced Mania: Meta-Analysis from Clinical Trials

Switching with different antidepressants: Post et al. 2006

Switch defined as a 2-point increase in manic severity score on CGI - Bipolar

Survival (proportion not switching to mania)

Time until switch (days)

Bupropion n = 51
Sertraline n = 58
Venlafaxine n = 65
Pharmacological treatments for bipolar depression

- Antidepressants
- Lithium
- Valproate
- Lamotrigine
- Antipsychotics
Pharmacological treatments for bipolar depression

- Antidepressants
- Lithium
- Valproate
- Lamotrigine
- Antipsychotics
Lamotrigine vs Placebo in Bipolar Depression: Acute Treatment

* *P<0.05 vs placebo. † *P<0.1 vs placebo.

Fig. 1 Lamotrigine compared with placebo: meta-analysis of randomised trials. (a) >50% reduction on Hamilton Rating Scale for Depression and (b) >50% reduction on Montgomery-Asberg Depression Rating Scale.

Pharmacological treatments for bipolar depression

- Antidepressants
- Lithium
- Valproate
- Lamotrigine
- Antipsychotics
Olanzapine + fluoxetine in bipolar depression

MADRS Change from Baseline

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 0

0 1 2 3 4 5 6 7 8

Week

Red markers p < .05 vs. OFC
p < .05 OLZ vs. PLA

Olanzapine (n=351)
Placebo (n=355)
OFC (n=82)

*MMRM = Mixed-Model Repeated Measures
F1D-MC-HGGY

Tohen M et al. Arch Gen Psychiatry 60:1079-1088, 2003
**Quetiapine monotherapy in bipolar depression**

Mean change in MADRS score from baseline (ITT)

**Study Week**

![Graph showing mean change in MADRS score from baseline (ITT) for Seroquel 600 mg/day, Seroquel 300 mg/day, and Placebo.]

***p<0.001 vs placebo for both active arms at all time points.

Mean baseline scores: BP I 30.5; BP II 30.2

MADRS Items: Change From Baseline

- 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

ITT, LOCF
EMBOLDEN I
Primary endpoint: change in MADRS total score

Study week

LSM change from baseline

Improvement

-20
-15
-10
-5
0
1 2 3 4 5 6 7 8

* Quetiapine 600 mg (n=263)
* Quetiapine 300 mg (n=255)
* Placebo (n=129)
* Lithium (n=136)

*p<0.05; **p<0.01; ***p<0.001 vs. placebo

ITT, LOCF
EMBOLDEN II
Primary endpoint: change in MADRS total score

Study week

EMBOLDEN II

Primary endpoint: change in MADRS total score

LSM change from baseline

Improvement

Quetiapine 600 mg (n=232)
Quetiapine 300 mg (n=229)
Placebo (n=121)
Paroxetine (n=118)

*p<0.05; **p<0.01; ***p<0.001 vs. placebo

ITT, LOCF
Acute Depression

- **First line**: SSRI plus antimanic agent
- **If on antimanic**: SSRI or quetiapine (if not on antipsychotic)
- **If recent unstable mood**: avoid antidepressants – increase antimanic and consider lamotrigine
  - NB avoid lamotrigine as a single first line agent in bipolar I but consider this in bipolar II
- **If doesn’t respond to SSRI**: switch to mirtazapine or venlafaxine or add quetiapine or olanzapine if not on an antipsychotic
- **Taper antidepressants** after symptoms reduced for 8 weeks
Treating Bipolar Depressive Episodes – an update

• Start with mood-stabilizing treatments
  ▪ Lamotrigine, quetiapine and OFC have best evidence vs placebo
  ▪ Lithium and valproate have some placebo-controlled data

• Antidepressants
  ▪ Patients not responding to mood stabilizing treatments or with convincing history of non-response
  ▪ Not alone
  ▪ Choice based on response history and side effect profile
BUT.....

- The management of bipolar disorder should take a long term perspective and not be driven simply by “fire-fighting”
Lithium v placebo, maintenance in bipolar disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurell 1968</td>
<td>2 / 4</td>
<td>5 / 6</td>
<td>4.4</td>
<td>0.20[0.01,3.66]</td>
</tr>
<tr>
<td>Coppen 1971</td>
<td>5 / 28</td>
<td>32 / 37</td>
<td>10.5</td>
<td>0.03[0.01,0.13]</td>
</tr>
<tr>
<td>Prien 1973b</td>
<td>12 / 39</td>
<td>17 / 22</td>
<td>11.3</td>
<td>0.13[0.04,0.44]</td>
</tr>
<tr>
<td>Prien 1973a</td>
<td>43 / 101</td>
<td>84 / 104</td>
<td>14.9</td>
<td>0.18[0.09,0.33]</td>
</tr>
<tr>
<td>Fieve 1976</td>
<td>22 / 38</td>
<td>33 / 43</td>
<td>12.9</td>
<td>0.42[0.16,1.08]</td>
</tr>
<tr>
<td>Kane 1982</td>
<td>5 / 25</td>
<td>19 / 24</td>
<td>10.2</td>
<td>0.07[0.02,0.26]</td>
</tr>
<tr>
<td>Glen 1984</td>
<td>5 / 12</td>
<td>8 / 9</td>
<td>5.8</td>
<td>0.09[0.01,0.96]</td>
</tr>
<tr>
<td>Prien 1984</td>
<td>33 / 75</td>
<td>40 / 73</td>
<td>14.8</td>
<td>0.65[0.34,1.24]</td>
</tr>
<tr>
<td>Bowden 2000</td>
<td>28 / 91</td>
<td>36 / 94</td>
<td>15.0</td>
<td>0.72[0.39,1.32]</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>155 / 413</td>
<td>274 / 412</td>
<td>100.0</td>
<td>0.21[0.10,0.43]</td>
</tr>
</tbody>
</table>

Chi-square 33.92 (df=8) P: 0.00  Z=-4.32 P: <0.00001
Lithium Not Clearly Superior to Placebo in Preventing Depression

Random effects $p = 0.10$

Effects of Rapid discontinuation of Li in BP-I Patients

Lithium and Valproate: 1 year Maintenance

- Divalproate (n=187)
- Placebo (n=94)
- Lithium (n=91)

* D < P, P < 0.02;

Bowden CL, et al. Arch Gen Psychiatry 2000
Long Term Treatments – Carbamazepine

Greil et al J Affect Disord 1997
Lamotrigine protection against depressive episodes: Combined analysis

39% increase in the percent of patients who remained intervention-free for depression at 18 months compared with placebo

LTG vs PBO, P=0.009

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

Goodwin et al. 2004 J. Clin. Psychiatry
Lamotrigine protection against manic episodes: Combined analysis

22% increase in the percent of patients who remained intervention-free for mania at 18 months compared with placebo.

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

Goodwin et al. 2004 J. Clin. Psychiatry
Olanzapine 12 month continuation in bipolar disorder

OLZ (n=225) 12 mg/day mean modal dose
PBO (n=136)

Bipolar Relapse Depressive Relapse Manic Relapse

- Bipolar Relapse: 80.1% OLZ vs. 46.7% PBO, p<0.01
- Depressive Relapse: 47.8% OLZ vs. 34.7% PBO, p=0.015
- Manic Relapse: 41.2% OLZ vs. 16.4% PBO, p<0.01

Divalproex versus Olanzapine

- Faster symptomatic relief from mania with olanzapine
- no difference in any measure of efficacy during maintenance period

Tohen et al Am J Psychiatry 2003
Aripiprazole 6 month continuation in bipolar disorder

Relapse Rates by Polarity

- Placebo (n=83)
- Aripiprazole (n=77)

*p=.009.

Quetiapine augmentation of depakote or lithium: Prevention of manic episode

Figure 2: Time to recurrence of a manic event (Kaplan-Meier curves; randomized treatment phase; ITT population; Study D1447C00126)

Vieta et al. 2007, ECNP
Quetiapine augmentation of depakote or lithium: Prevention of depressive episode

Figure 3: Time to recurrence of a depressive event (Kaplan-Meier curves; randomized treatment phase; ITT population; Study D1447C00126)

Vieta et al. 2007, ECNP
Long-term Treatment: What?

- First line: lithium, olanzapine or valproate
- If fails monotherapy over 6 months
  - Li + valp, Li + olanz, Valp + olanz
- If combination fails
  - Consider lamotrigine (esp. BPII), carbamazepine, referral to tertiary centre
- NOT antidepressants routinely (unless no mania X 5 yrs)
- Normally treat for at least 5 years
Key Points

• Bipolar disorder is more common than you may think
• There is little data for the most common form – BPII
• There are many treatment options for mania and they all have similar effect sizes
• How to manage BP depression is not clear
  ▪ Antidepressants (SSRIs) may not work
  ▪ Quetiapine, lamotrigine and OFC have the best evidence
• Long term treatment is THE KEY
  ▪ Lithium, valproate, olanzapine and aripiprazole all work but best in preventing mania
  ▪ Lamotrigine better for prevention of depression (than mania)
  ▪ Quetiapine prevents both depression and mania?