Guidelines for the Pharmacological Management of Bipolar Disorder

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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
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    • Astra Zeneca, Eli Lilly and Wyeth
BAP Guidelines for the Management of Bipolar Disorder

G.M. Goodwin “Evidenced based guidelines for treating bipolar disorder: recommendations from the BAP.” J Psychopharmacology 17(2) 2003 149-173
NICE Clinical Guideline
July 2006

Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care
Practice Guidelines for the Treatment of Patients with Bipolar Disorder

Hirschfeld et al., Am. J. Psychiatry 2002
The Texas Implementation of Medication Algorithms (TIMA): Update to the algorithms for treatment of bipolar I disorder

Guidance

- Common aspects of care for all people with bipolar disorder
- Assessment, recognition and diagnosis
- Treatment setting and pathways to care
- Physical care
- Treatment and management of bipolar disorder
- Long-term management
- Treatment and management of women of child-bearing potential
- Assessment, diagnosis and treatment of children and adolescents
Guidance

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- Assessment, diagnosis and treatment of children and adolescents
Common aspects of care

- Information and informed consent
  - Provide good information re disorder
  - Collaborative working
  - Information about self-help groups
- Psychological principles
  - Therapeutic relationship
  - Identify early warning signs
  - Advice re life style
- Appropriate language and written material
- Support for families
- Advanced statements
- Comorbid personality disorder
- Drugs and alcohol
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Treatment setting and pathways to care

- Long-term illness needing long-term care
- Integrated primary / secondary care programmes
- Primary care registers and telephone support
- CMHTs for:
  - Problems engaging with services, poor adherence
  - Frequent relapses, poor symptom control, poor functioning, comorbid anxiety
  - Substance misuse
  - Significant risk
- EIP, CAT, AO, IP, day hospitals, rehab. should all be available
- Trusts providing specialist mental health care should ensure that clinicians have access to specialist advice
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Physical care

● At presentation
  ● Smoking and alcohol history
  ● Renal function, LFTs, TFTs, FBC, Glucose, lipids
  ● BP, height and weight
  ● Consider ECG, CXR, drug screening, EEG, CT, MRI

● Annual review

● Management of weight gain
  ● Diet, exercise, diet clinic, dietician
  ● Sibutramine and topiramate NOT recommended
Physical care

- **Antipsychotics**
  - At initiation: wt, ht, gluc, lipids, (ECG and prolactin)
  - Monitoring: wt every 3/12 for 1 yr, gluc and lipids at 3/12 (olanz at 1/12), prolactin if indicated
  - Be aware of NMS and DKA

- **Lithium**
  - Not for primary care
  - Warn re probs of stopping
  - Renal, TFT, ht and wt (ECG, FBC)
  - Levels 0.6 – 0.8 (or 0.8 – 1.0 if poor response)
  - Warn re NSAIDs
Physical care

- **Valproate**
  - At initiation and 6/12: Ht, wt, FBC, LFTs
  - Not for women under 18 or of child bearing potential
  - Levels if ineffective, poor adherence or toxicity

- **Lamotrigine**
  - Slow titration (N.B. S-JS)
  - Beware interaction with OCP

- **Carbamazepine**
  - Only on specialist advice
  - At initiation: FBC, LFTs, ht and wt (repeat at 6/12 with U&Es)
  - Levels every 6 months
  - Beware interaction with OCP
Guidance

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- Assessment, diagnosis and treatment of children and adolescents
The course of Bipolar Disorder

Mania

Hypomania

Euthymia

Minor Depression

Major Depression

Preliminary Phase

Preventative Phase
Valproate and Lithium in acute mania
Bowden et al 1994

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25%</td>
</tr>
<tr>
<td>Lithium</td>
<td>49%*</td>
</tr>
<tr>
<td>Depakote</td>
<td>48%**</td>
</tr>
</tbody>
</table>

* p=0.025
** p=0.004

N.B. Efficacy of Depakote independent to prior responsiveness to Lithium
Gabapentin vs Placebo

YMRS Scores (observed cases)

Compared to placebo, olanzapine patients had a statistically significantly greater LOCF mean improvement at week 1 which was maintained throughout the study.
**Treatment-Emergent Parkinsonism†:**
Categorical Analysis of Simpson-Angus Scale

- Placebo: 12.0% (11/92), P=.065
- Olanzapine: 11.9% (23/194), P=.176
- Haloperidol: 6.9% (8/116), P<.001*
- Olanzapine: 14.5% (218/1501), P=.038**

*Haloperidol was associated with significantly higher rates of EPS in the bipolar group.
**Olanzapine was associated with significantly lower rates of EPS in the bipolar group.
†Defined as a score on the Simpson-Angus Scale of ≤3 at baseline >3 anytime thereafter.
Quetiapine: Mania, acute treatment

Change from baseline (YMRS)

Day

Study 104 + 105

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

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

**RIS-USA-239**

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

**RIS-IND-002**

- Median dose 6mg/day
- BL: Risperidone = 37.4; placebo = 37.0

LOCF analysis; *P*<0.001 risperidone vs placebo; Hirschfeld RM, et al. Am J Psychiatry 2004;161:1057–65

LOCF analysis; *P*<0.01 risperidone vs placebo; Khanna et al. Brit J Psychiatry 2005;187, 229-34
Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS

*P<0.01 vs placebo, LOCF analysis.

Keck et al.; *Am J Psych*, in press
# 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>
</tr>
<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 monotherapy** | **Favours cotherapy**
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
Acute Mania:
Those on anti-manic treatment

- Optimise treatment
  - Li level 0.8-1.0
  - Valproate to max. licensed dose (depending on SEs)
  - Don’t generally increase carbamazepine
- Add olanzapine, risperidone or quetiapine
Guideline Evolution: Acute mania

- Place of antipsychotics has changed:
  - Only in combination (APA)
  - Alternative to Li or valproate (BAP, TIMA)
    - NB olanzapine “1B” in TIMA
    - Main first line option (NICE)
- Valproate has had extra cautions added by NICE
- Carbamazepine has been downgraded
  - level “1B” (TIMA)
  - Only on specialist recommendation (NICE)
- Second line fairly consistent
  - Li or valproate + atypical
Depression is **THE** Problem

Bipolar I

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

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

Bipolar II

- Asymptomatic: 46%
- Symptomatic: 54%
- Depressed: 94%
- Hypomaniac: 2%
- Mixed: 4%

(Judd LL et al. *Archives of General Psychiatry* 60:261-269, 2003)
**Antidepressants and bipolar disorder**

<table>
<thead>
<tr>
<th>Antidepressant vs Placebo (5 trials)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 1.86 (1.49-2.3); NNT 4.2; superiority achieved</td>
</tr>
<tr>
<td><strong>Switching into Mania/Hypomania</strong></td>
<td>OR 1.00 (.47-2.13); Rates 3.8% vs 4.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TCA vs other Antidepressants</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 0.8 (.76-1.06); equivocal inferiority</td>
</tr>
<tr>
<td><strong>Switching into Mania/Hypomania</strong></td>
<td>OR 2.92 (1.28-6.71); Rates 10% vs 3.2%</td>
</tr>
</tbody>
</table>

Gijsman et al Am J Psychiatry 2004
Lamotrigine vs Placebo in Bipolar Depression: Acute Treatment

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

Olanzapine + fluoxetine in bipolar depression

![Graph showing MADRS change from baseline over weeks for Olanzapine (n=351), Placebo (n=355), and OFC (n=82).]

- Red markers: p < .05 vs. OFC
- Green markers: p < .05 OLZ vs. PLA

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

Tohen M et al. Arch Gen Psychiatry 60:1079-1088, 2003
OFC vs lamotrigine in BPI Depression
Brown et al. 2006 J Clin Psychiatry 67;1025-33

Figure 1. Change From Baseline to Each Treatment Visit in Mean CGI-S Total Score (with 95% confidence interval bars) \(^a\)

Note:
- Small difference in effect
- OFC associated with more AEs, weight gain and metabolic changes than lamotrigine
- N= 205 each arm
Quetiapine monotherapy in bipolar depression

Mean change in MADRS score from baseline (ITT)

***p<0.001 vs placebo for both active arms at all time points
Mean baseline scores: BP I 30.5; BP II 30.2

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

MADRS Items: Change From Baseline

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)

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 mirtazepine or venlafaxine or add quetiapine or olanzapine if not on an antipsychotic
- Taper antidepressants after symptoms reduced for 8 weeks
Guideline Evolution: Acute Depression

• Much less consensus:
  - Don’t use antidepressant monotherapy esp. in bipolar I

• Change in views over lamotrigine
  - Consider if antidepressants lead to problems (BAP)
  - First line (APA and TIMA)
  - Not first line or single agent in BPI (NICE)

• Increasing role for antipsychotics
  - Consider, esp if psychotic (BAP)
  - Quetiapine and OFC second line (TIMA)
  - Quetiapine possible alternative to SSRI (NICE)
Guidance

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Relationship between cycle length and number of episodes

- Kraepelin, 1921
- Zis et al, 1980
- Angst, 1981
- Roy-Byrne et al, 1985

Cycle Length (Months) vs. Episode
Mood Disorders: Risk of relapse

Bipolar Disorder, constant risk of relapse over 40yrs; 0.4episodes/ year

Long-term Treatment: When?

- Single manic episode with significant risk/consequences
- 2+ episodes in bipolar I
- In bipolar II if:
  - Significant risk
  - Frequent episodes
  - Significant functional impairment
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>Bowdren 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>Subtotal(95%CI)</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

FIGURE 3. Randomized, Placebo-Controlled Trials Assessing the Effectiveness of Lithium for the Prevention of Depressive Relapse in Bipolar Disorder Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Risk Ratio (95% CI)</th>
<th>Lithium Relapse Rate</th>
<th>Placebo Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al. 1982 (12)</td>
<td>0.40 (0.10–1.56)</td>
<td>20% (N=2 of 10)</td>
<td>50% (N=6 of 12)</td>
</tr>
<tr>
<td>Bowden et al. 2000 (13)</td>
<td>0.62 (0.29–1.34)</td>
<td>10% (N=9 of 91)</td>
<td>16% (N=15 of 94)</td>
</tr>
<tr>
<td>Bowden et al. 2003 (14)</td>
<td>0.54 (0.29–1.01)</td>
<td>22% (N=10 of 46)</td>
<td>40% (N=26 of 70)</td>
</tr>
<tr>
<td>Bowden et al. 2002 (15)</td>
<td>0.98 (0.71–1.35)</td>
<td>38% (N=46 of 121)</td>
<td>39% (N=47 of 121)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.72 (0.49–1.07)</td>
<td>25% (N=67 of 268)</td>
<td>32% (N=96 of 297)</td>
</tr>
</tbody>
</table>

*Risk Ratio (random effects, logarithmic scale)*

The area of the blue box represents the weighting given to the trial in the overall pooled estimate and takes into account the number of participants and events and the amount of between-studies variation (heterogeneity).

Lower confidence interval extends beyond graph (0.10).

Random effects \( p = 0.10 \)

Efficacy of depakote in prophylaxis of bipolar disorder

Time to mania relapse or depression in patients with history of psychiatric hospitalization & last episode ≤ 1 year
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

* 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.

LTG vs PBO, \( P=0.034 \)

Goodwin et al. 2004 J. Clin. Psychiatry
Lamotrigine long term treatment in rapid cycling BP disorder

Lamotrigine vs. Placebo
Overall Survival BPI (n = 125)

Survival Estimate vs. Week

Placebo
Lamotrigine


\[ P = 0.426 \]
Lamotrigine vs. Placebo
Overall Survival BP II (n = 52)


![Graph showing survival estimates for Lamotrigine vs. Placebo](image)

- **Placebo**: 4 weeks
- **Lamotrigine**: 15 weeks

Median Survival

- Placebo: 4 weeks
- Lamotrigine: 15 weeks

*p = 0.015*
Olanzapine continuation in bipolar disorder

Long Term Treatments – Olanzapine vs lithium for mania

Olanzapine (mean dose: 11.9 mg)

Lithium (mean dose: 1103 mg
[mean level = 0.77])

P<0.001.
Long Term Treatments – Olanzapine vs lithium for depression

**Graph:***

- **Probability of Remaining in Remission (%):**
- **Time to Relapse Into Depression (days):**

- **Olanzapine (mean dose: 11.9 mg):**
- **Lithium (mean dose: 1103 mg [mean level = 0.77]):**

**Statistical Information:**

- \( P = 0.889. \)
26 week trial of aripiprazole in recently manic BPI patients (Keck et al. 2006)

Figure 5. Distribution of Relapses by Type in the Placebo Group and the Aripiprazole Group During the Double-Blind Phase

![Distribution of Relapses by Type](image)

* *p = .009; time to manic relapse significantly different.*

Figure 4. Time From Randomization to (A) Manic Relapse and (B) Depressive Relapse

![Time From Randomization](image)

Abbreviations: CI = confidence interval, HR = hazard ratio.
Lithium and/or Carbamazepine Maintenance Response

Randomized (double blind) to Li+ or CBZ for 1 year, then to other, then to both

* p<.05 if RC hx

Percent CGI Responders

N = 42

N = 35

N = 29

Lithium

CBZ

Both*

All patients

Hx of rapid-cycling
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
Guideline Evolution: Long term treatment

- Variations in guidelines due to poor evidence base
- Change in role of antipsychotics
  - Withdraw antipsychotics used in acute episode (APA)
  - Olanzapine as alternative to Li (BAP)
  - Atypical first line (NICE)
- Lithium down graded
  - First line (APA, BAP, TIMA – after mania)
  - Second line (NICE)
- Valproate down graded
  - First line (APA, TIMA – after mania)
  - Consider after Li (BAP)
  - Concern in women (NICE)
- Carbamazepine down graded
  - First line (APA)
  - Poor alternative to Li (BAP)
  - Third or fourth line (TIMA)
  - On specialist advice (NICE)
- Increased caution recommended re use of antidepressants
- NICE emphasise the need for physical health monitoring
The course of Bipolar Disorder

- Mania
- Hypomania
- Euthymia
- Minor Depression
- Major Depression

Preliminary Phase Preventative Phase
The course of Bipolar Disorder

Mania

Hypomania

Euthymia

Minor Depression

Major Depression

Preliminary Phase

Preventative Phase

“The study of MEDICINE is prosecuted under two relations, namely as a Science and as an Art”

The Science and Practice of Medicine
W. Aitken
1872
Annual Residential Meeting
of the Faculty of
General and Community Psychiatry

The Science and Practice of Psychiatry
Twin themes: Vulnerability and Service Delivery

Hilton Hotel and Sage Gateshead
Newcastle Gateshead
18-19th October 2007