Relapse prevention in bipolar disorder
Objectives

• To review outcomes and clinical need in bipolar disorder
• To review evidence for relapse prevention
• To review the relationship between treatment adherence and outcome in bipolar disorder
• To consider how better medicines management could aid adherence to treatment
Bipolar Disorder

• Lifetime prevalence approx 1%
• Using estimates of
  – Years of life lost
  – Years lived with disability

BPD ranked by WHO as 6th leading cause of disability worldwide

National Collaborating Centre for Mental Health
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
National Clinical Practice Guideline Number 38, Full Guideline
Outcomes after first episode of mania

1st episode of mania

Discharged From Hospital

Syndromal recovery
(diagnostic criteria no longer met)
98%

Symptomatic recovery
(depression or mania ratings within normal range)
72%

Functional recovery
(regaining previous occupational and residential status)
43%

Status within 2 years

New episode of mania
20%

New episode of depression
20%


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Long-term symptomatic status

Bipolar-1

- Asymptomatic: 53%
- Symptomatic: 47%

Symptoms:
- Depressed: 67%
- Manic/hypomaniac: 20%
- Mixed: 13%

Judd LL, Akiskal HS, Schettler PJ et al. The long-term natural history of the weekly symptomatic status of Bipolar I Disorder. Arch Gen Psychiatry 2002;59:530-37
Bipolar-2

Symptomatic 54%
Asymptomatic 46%

Depressed 94%
Hypomanic 2%
Mixed 4%

Judd LL, Akiskal HS, Schettler PJ et al.
A prospective investigation of the natural history of the long-term weekly symptomatic status of Bipolar II Disorder
Arch Gen Psychiatry 2003;60:261-269
Premature death

- Standardised mortality ratio in bipolar disorder for death by natural causes
  - Males = 1.9
  - Females = 2.1

SUICIDE

- Bipolar 1
  - About 17% of sufferers will attempt suicide
- Bipolar 2
  - About 24% of sufferers will attempt suicide
- Standardised mortality ratio
  - 15 for men
  - 22.4 for women
- Most suicide attempts occur in depressive phase

National Collaborating Centre for Mental Health
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
National Clinical Practice Guideline Number 38, Full Guideline

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Costs of BPD

- Annual cost to UK economy £5.2 billion (2006 prices)
- Greatest costs associated with unemployment & loss of productivity
- NHS costs approx £1.6 billion
Bipolar Disorder: Cost of Care

<table>
<thead>
<tr>
<th>Category</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatrist</td>
<td>32.1%</td>
</tr>
<tr>
<td>Inpatient</td>
<td>9.9%</td>
</tr>
<tr>
<td>CMHN</td>
<td>6.7%</td>
</tr>
<tr>
<td>Day care</td>
<td>6.1%</td>
</tr>
<tr>
<td>Residential care</td>
<td>5.2%</td>
</tr>
<tr>
<td>Therapist</td>
<td>3.7%</td>
</tr>
<tr>
<td>GP</td>
<td>2.2%</td>
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<tr>
<td>Other doctor</td>
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<tr>
<td>Social worker</td>
<td>2.2%</td>
</tr>
<tr>
<td>Medicines</td>
<td>2.2%</td>
</tr>
<tr>
<td>Informal care</td>
<td>27.9%</td>
</tr>
</tbody>
</table>

Paying the price: the cost of mental health care in England to 2026
London, King’s Fund, 2008
Clinical need in bipolar disorder

• Effective treatment for acute episodes
  – Mania
  – Hypomania
  – Depression

• Which is also effective in preventing relapse:
  – Mania / hypomania
  – Depression
What do treatment Guidelines tell us?

Bipolar disorder
The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

BAP Guidelines

Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology

GM Goodwin University Department of Psychiatry, Warneford Hospital, Oxford OX1 7JX, UK.
Consensus Group of the British Association for Psychopharmacology

Abstract
The British Association for Psychopharmacology guidelines specify the scope and target of treatment for bipolar disorder. The second version, like the first, is based explicitly on the available evidence and presented, like previous Clinical Practice guidelines, as recommendations to aid clinical decision making for practitioners: they may also serve as a source of information for patients and carers. The recommendations are presented together with a more detailed and selective qualitative review of the available evidence. A consensus meeting, involving experts in bipolar disorder and its treatment, reviewed key areas and considered the strength of evidence and clinical implications. The guidelines were drawn up after extensive feedback from participants and interested parties. The strength of supporting evidence was rated. The guidelines cover the diagnosis of bipolar disorder, clinical management, and strategies for the use of medicines in treatment of episodes, relapse prevention and stopping treatment.

Key words
antidepressants; antipsychotics; bipolar disorder; CBT; depression; evidence-based guidelines; lithium; mood stabilizers; treatment
1.5.1.2 Lithium, olanzapine or valproate should be considered for long-term treatment of bipolar disorder. The choice should depend on:

- response to previous treatments
- the relative risk, and known precipitants, of manic versus depressive relapse
- physical risk factors, particularly renal disease, obesity and diabetes
- the patient’s preference and history of adherence
- gender (valproate should not be prescribed for women of child-bearing potential)
- a brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people.
Maintenance treatment

Intensive monitoring requested only for BP depression and preventing recurrence in BP disorder.
Mood stabilisers in bipolar-1: the BALANCE trial

Hazard ratios for the primary outcome:
Combination therapy Vs. valproate 0·59 (p=0·0023)
Lithium Vs. valproate 0·71 (p<0.05)
Combination therapy Vs. lithium 0·82 (p=0·27)
Aripiprazole vs placebo in prevention of manic relapse (100 Weeks)

Relapse = Discontinuation of the study attributed to lack of efficacy indicated by hospital admission because of a manic episode or addition to or increase in psychotropic medication other than study drug for manic and/or depressive symptoms. Mean dose of aripiprazole during last 7 days of treatment, whenever that occurred, was 24.1 mg/day HR = hazard ratio (safety sample); CI = confidence interval

Keck PE, Calabrese JR, McIntyre RS et al.
Olanzapine vs placebo in prevention of manic relapse: (48 Weeks)

Tohen M, Calabrese J, Sachs G et al. Randomized, Placebo-Controlled Trial of Olanzapine as Maintenance Therapy in Patients With Bipolar I Disorder Responding to Acute Treatment With Olanzapine Am J Psychiatry 2006; 163:247–256
Quetiapine vs lithium & placebo in prevention of recurrence: (104 Weeks)

Figure 2. Time to recurrence of any mood event during randomized phase (Kaplan-Meier curves, ITT population)

Weisler R, Nolen W, Neijber A et al.
Quetiapine or lithium versus placebo for maintenance treatment of bipolar I disorder after stabilization on quetiapine
Poster presented at the 8th International Conference on Bipolar Disorder 2009, Pittsburgh, USA
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder

Dina Popovic · Maria Reinares · Benedikt Amann · Manel Salamero · Eduard Vieta

Received: 30 July 2010 / Accepted: 8 October 2010
© Springer-Verlag 2010

Abstract
Rationale Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments. Objective The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of BD by means of the number needed to treat (NNT).
Methods The efficacy of drugs used for maintenance treatment of BD, as emerging from the results of randomized controlled trials, was assessed using the size effect measure of NNT. PubMed searches were conducted on English-language articles published until May 2010 using the search terms “bipolar disorder,” “mania,” “mixed episode,” or “bipolar depression,” cross-referenced with trial characteristic search phrases and generic names of medications. The search was supplemented by manually reviewing reference lists from identified publications.
Results In 15 studies, aripiprazole, olanzapine, quetiapine, risperidone long-acting injection, lithium, lamotrigine, and divalproex proved effectiveness in terms of NNTs (≥10% advantage over placebo) for prevention of relapse into any mood episode. Quetiapine, lithium, risperidone long-acting injection, aripiprazole, and olanzapine are effective in manic recurrence prevention. Lamotrigine, quetiapine, and lithium present significant NNTs for prevention of depressive relapses.
Conclusions All of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for prevention of manic and/or depressive relapses. The comparison of NNT values of the available agents may represent a useful tool in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with BD.

Keywords Bipolar disorder · NNT · Treatment efficacy · Maintenance treatment
Number Needed To Treat: NNT

- Based on absolute difference in outcomes between treatments

- The **NNT** is an **estimate** of the number of patients that would need to be given a treatment for **one additional patient** to achieve the desired outcome who **would not have achieved it with a control treatment**.

- NNTs express the "**therapeutic effort**" needed to achieve the desired outcome
Interpreting NNTs

- Only NNTs <10 are clinically meaningful.
- Lower NNTs reflect larger differences between treatment groups.

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>Corresponding NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large (&gt;0.8)</td>
<td>NNT 3</td>
</tr>
<tr>
<td>Medium (0.5)</td>
<td>NNT 4</td>
</tr>
<tr>
<td>Small (0.2)</td>
<td>NNT 9</td>
</tr>
</tbody>
</table>

Popovic D, Reinares M, Amann B et al.  
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder  
Psychopharmacology 2011;213:657-667  
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## NNTs for prevention of manic episode (vs placebo)

<table>
<thead>
<tr>
<th>Drug</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine *</td>
<td>24</td>
<td>5 - infinity</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>59</td>
<td>10 - infinity</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>26</td>
<td>8.6 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>4</td>
<td>2.5 - 6.4</td>
</tr>
<tr>
<td>Lithium</td>
<td>8</td>
<td>4.6 - 16.3</td>
</tr>
<tr>
<td>Lithium</td>
<td>6</td>
<td>3 - 26.4</td>
</tr>
<tr>
<td>Lithium</td>
<td>14</td>
<td>6.3 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>69</td>
<td>7.5 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>3</td>
<td>2.2 - 2.7</td>
</tr>
<tr>
<td>Valproate</td>
<td>22</td>
<td>6.8 - infinity</td>
</tr>
</tbody>
</table>

*Lamotrigine is licensed in the prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes.*

---

Popovic D, Reinares M, Amann B et al.
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder
Psychopharmacology 2011;213:657-667

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## NNTs for prevention of manic episode

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration (weeks)</th>
<th>NNT</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>100</td>
<td>7</td>
<td>3.6 – 24.9</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ MS vs placebo</td>
<td>48</td>
<td>12</td>
<td>3.4 - infinity</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>72</td>
<td>5</td>
<td>3.4 – 8.8</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ MS vs placebo</td>
<td>104</td>
<td>7</td>
<td>4.8 – 10.1</td>
</tr>
<tr>
<td>+ MS vs placebo</td>
<td>104</td>
<td>9</td>
<td>5.7 - 14</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>104</td>
<td>3</td>
<td>2 – 2.8</td>
</tr>
</tbody>
</table>

Popovic D, Reinares M, Amann B et al.  
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder  
Psychopharmacology 2011;213:657-667
Inevitable switch to bipolar depression?

Long-term symptomatic status

Bipolar-1

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

Depressed: 67%

Number of changes in mood polarity / year = 3.5

Bipolar-2

- Asymptomatic: 46%
- Symptomatic: 54%
- Hypomorphic: 2%
- Mixed: 4%

Depressed: 94%

Number of changes in mood polarity / year = 1.3

Judd LL, Akiskal HS, Schettler R et al.
A prospective investigation of the natural history of the long-term weekly symptomatic status of Bipolar II Disorder.
Arch Gen Psychiatry 2003;60:261-69

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Treatment for chronic and recurrent depressive symptoms

1.5.1.9 The following treatments should be considered, in discussion with the patient, for people who have an established diagnosis of bipolar disorder and chronic or recurrent depressive symptoms, but who are not taking prophylactic medication and have not had a recent manic or hypomanic episode:

- long-term treatment with SSRIs at the minimum therapeutic dose in combination with prophylactic medication
- cognitive behavioural therapy (16–20 sessions) in combination with prophylactic medication
- quetiapine*, or
- lamotrigine*.

Not all agents are licensed in this setting in the UK
BAP Guideline 2009

Maintenance treatment

Figure 3 Long term treatment scheme—maintenance therapy.
Lamotrigine

Maintenance after bipolar depression

- Patients recently recovered from major depressive episode
- Randomised, double-blind placebo controlled trial
  - Lamotrigine 50, 200 or 400mg/day n= 221
  - Lithium (0.8 – 1.1 mmol/l) n = 121
    - Mean serum level 0.8mmol/l
  - Placebo n = 121
- Primary outcome measure:
  - Time to intervention with other treatment for mood instability
    - Antidepressant, other mood stabiliser, antipsychotic

Calabrese JR, Bowden CL, Sachs GS, et al.
A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar-I disorder
Journal of Clinical Psychiatry 2003;64:1013-24
Results

Lamotrigine v lithium/placebo in maintenance after bipolar depression

% of patients still well after one year

* = 0.028 vs placebo
** = 0.026 vs placebo

Adapted from: Calabrese JR, Bowden CL, Sachs GS, et al.
Lamotrigine in bipolar depression

• Licensed for prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes

• Not licensed for the acute treatment of bipolar depression in UK

• Slow titration mandatory:
  – Initial dose 25mg once daily for two weeks, then 50mg once daily for two weeks. Then increase dose by a maximum of 50mg-100mg every 1-2 weeks until the optimal response is achieved
  – Effective dose in RCTs: 200mg/day
N-Desalkylquetiapine, a Potent Norepinephrine Reuptake Inhibitor and Partial 5-HT$_{1A}$ Agonist, as a Putative Mediator of Quetiapine’s Antidepressant Activity

Niels H Jensen$^1$, Ramona M Rodriguez$^{2,3}$, Marc G Caron$^{4,5}$, William C Wetsel$^{2,3,4,5}$, Richard B Rothman$^6$ and Bryan L Roth$^6,1,7,8$

$^1$Department of Pharmacology, University of North Carolina Medical School, Chapel Hill, NC, USA; $^2$Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; $^3$Mouse Behavioral and Neuroendocrine Analysis Core Facility, Duke University Medical Center, Durham, NC, USA; $^4$Department of Cell Biology, Duke University Medical Center, Durham, NC, USA; $^5$Department of Neurology, Duke University Medical Center, Durham, NC, USA; $^6$Intramural Research Program, NIDA, Clinical Psychopharmacology Section, NIH, Baltimore, MD, USA; $^7$Department of Psychiatry, Comprehensive Cancer Center, Center for Neurobiology Division of Medicinal Chemistry and Natural Products, NIMH Psychoactive Drug Screening Program, University of North Carolina Medical School, Chapel Hill, NC, USA

Quetiapine is an atypical antipsychotic drug that is also US FDA approved for treating bipolar depression, albeit by an unknown mechanism. To discover the potential mechanism for this apparently unique action, we screened quetiapine, its metabolite N-Desalkylquetiapine, and dibenzo[b,e][1,4]thiazepine-11(10-f)-one (DBTO) against a large panel of G-protein-coupled receptors, ion channels, and neurotransmitter transporters. DBTO was inactive at all tested molecular targets. N-Desalkylquetiapine had a high affinity (3.4nM) for the histamine H$_1$ receptor and moderate affinities (10–100 nM) for the norepinephrine reuptake transporter (NET), the serotonin 5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{3}$, receptors, the a$_{1B}$/a$_{1D}$-adrenergic receptor, and the M$_1$, M$_3$, and M$_5$ muscarinic receptors. The compound had low affinities (100–1000 nM) for the 5-HT$_{1D}$, 5-HT$_{2C}$, 5-HT$_{3}$, 5-HT$_{5}$, 5-HT$_{6}$, a$_{2A}$, a$_{2B}$, a$_{2C}$, H$_2$, M$_2$, M$_4$, and dopamine D$_1$, D$_2$, D$_3$, and D$_4$ receptors. N-Desalkylquetiapine potently inhibited human NE transporter with $K_i$ of 12nM, about 10-fold more potent than quetiapine itself. N-Desalkylquetiapine was also 10-fold more potent and more efficacious than quetiapine at the 5-HT$_{1A}$ receptor. N-Desalkylquetiapine was an antagonist at 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, 5-HT$_{3}$, a$_{1A}$, a$_{1D}$, a$_{2A}$, a$_{2C}$, H$_1$, M$_1$, M$_3$, and M$_5$ receptors. In the mouse tail suspension test, N-Desalkylquetiapine displayed potent antidepressant-like activity in VMAT2 heterozygous mice at doses as low as 0.1 mg/kg. These data strongly suggest that the antidepressant activity of quetiapine is mediated, at least in part, by its metabolite N-Desalkylquetiapine through NET inhibition and partial 5-HT$_{1A}$ agonism. Possible contributions of this metabolite to the side effects of quetiapine are discussed.

Neuropsychopharmacology (2008) 33, 2303–2312; doi:10.1038/sj.npp.1301646; published online 5 December 2007

Keywords: quetiapine; N-Desalkylquetiapine; norepinephrine reuptake inhibitor; antidepressant; antipsychotic
Objectives
• To evaluate efficacy of quetiapine (300 or 600mg/day) in treatment of depression in bipolar 1 & 2 disorder
• To evaluate quetiapine in time to recurrence of a mood episode (depressive or manic)

Patients
• Outpatients with bipolar 1 or 2
• Rapid cycling NOT excluded
• Major depressive episode
  – Duration <1 year, onset >4 weeks

Design
• 8 week double-blind, placebo controlled trial
• Primary outcome measure change in MADRS total score followed by
• 26-52 week continuation phase

Active control arms
• Lithium (Embolden 1)
• Paroxetine (Embolden 2)
A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN I)

AH Young, S McElroy, W Chang, B Olausson, B Paulsson, M Brecher

Figure 5. Time to recurrence of a mood event in patients with bipolar I or II disorder (ITT, LOCF; Continuation Treatment Phase)

HR: 0.056, 95% CI: 0.39 to 0.82

Proportion of patients event free

Time to event (days)

Quetiapine (n=163)
Placebo (n=165)
A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN II)

S McElroy, B Olausson, W Chang, A Nordenhem, B Paulsson, M Brecher, AH Young

Figure 5. Time to recurrence of a mood event in patients with bipolar I or II disorder (ITT, LOCF; Continuation Treatment Phase)

HR: 0.43; 95% CI: 0.27 to 0.69

Proportion of patients event free

Time to event (days)

Quetiapine (n=127)  
Placebo (n=129)
### NNTs for prevention of depressive episode (vs placebo)

<table>
<thead>
<tr>
<th>Drug</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>7</td>
<td>3.3 - 38.5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>28</td>
<td>6.9 - infinity</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>20</td>
<td>7.2 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>22</td>
<td>7.6 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>49</td>
<td>8.4 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>13</td>
<td>4.1 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>86</td>
<td>7.4 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>17</td>
<td>6.4 - infinity</td>
</tr>
<tr>
<td>Lithium</td>
<td>4</td>
<td>2.8 - 4.4</td>
</tr>
<tr>
<td>Valproate</td>
<td>11</td>
<td>5.6 - 74.3</td>
</tr>
</tbody>
</table>

*Not licensed for prevention of depressive episodes in bipolar disorder in the UK

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Popovic D, Reinares M, Amann B et al.  
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder  
Psychopharmacology 2011;213:657-667
# NNTs for prevention of depressive episode

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>NNT</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>Monotherapy vs placebo</td>
<td>50</td>
<td>7.7 – infinity</td>
</tr>
<tr>
<td></td>
<td>+ MS vs placebo + MS</td>
<td>6</td>
<td>2.6 - infinity</td>
</tr>
<tr>
<td></td>
<td>Monotherapy vs placebo</td>
<td>12</td>
<td>5.3 - infinity</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>+ MS vs placebo + MS</td>
<td>6</td>
<td>2.6 - infinity</td>
</tr>
<tr>
<td></td>
<td>Monotherapy vs placebo</td>
<td>12</td>
<td>5.3 - infinity</td>
</tr>
<tr>
<td></td>
<td>+ MS vs placebo + MS</td>
<td>6</td>
<td>3.9 – 7.7</td>
</tr>
<tr>
<td></td>
<td>Monotherapy vs placebo</td>
<td>4</td>
<td>2.8 – 4.2</td>
</tr>
</tbody>
</table>

*Not all agents licensed in this setting in the UK*

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Psychopharmacology 2011;213:657-667  
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### Licensed indications in the treatment of bipolar disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment of acute episodes</th>
<th>Prevention of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manic episode</td>
<td>Depressive episode</td>
</tr>
<tr>
<td>ARIPIPRAZOLE</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>ASENAPINE</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>OLANZAPINE</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>RISPERIDONE</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>


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Revolving door = vicious cycle

Delay in treating first episode

Treatment response but subsequent poor adherence to treatment

Progression to chronic illness and/or treatment resistance

Relapse & need to re-establish treatment
BPD: Poor treatment adherence

- Rates of non-adherence range from 20%-60% in bipolar disorder
- In one study where 33% of patients showed poor adherence:

<table>
<thead>
<tr>
<th>Poor adherence</th>
<th>Good adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>- hospitalisation rates 73%</td>
<td>- hospitalisation rates 31%</td>
</tr>
<tr>
<td>- average length of hospital stay 37 days</td>
<td>- average length of hospital stay 4 days</td>
</tr>
</tbody>
</table>

Is complexity of treatment regimen important in BPD?

• Consider
  – Need for combination treatments
  – Frequency of dosing
  – Intrusion into patient’s lifestyle
  – Impact on adherence / outcome
Once-daily dosing improves adherence

Systematic review of MEMS literature 1986 – 2007

(Range of chronic physical & neurological illnesses
No psychiatric illnesses were included in this analysis)

Once daily dosing:

• 13%-26% better adherence than bd dosing
• 22%-41% better adherence than tid dosing

Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC.
Effect of medication dosing frequency on adherence in chronic diseases
Am J Manag Care 2009;15:e22-33
Quetiapine-IR & Quetiapine-XL: psychiatric hospital admissions in patients with bipolar-1 disorder

- Retrospective analysis of US managed care database using administrative claims data
- 190 patients with bipolar-1 disorder who had prescription claims data for both Quetiapine-IR and Quetiapine-XL
- 6-month treatment period on Quetiapine-IR
- Followed by 6-month treatment period on Quetiapine-XL
- Differences in hospital admissions and costs pre- and post-switch
- Dose was not recorded in the original protocol

Mean mental health hospital admission costs per patient/6 months:
- Quetiapine IR = $2835
- Quetiapine XL = $776

\( p = 0.0019 \)

Adapted from: Hassan M, Pelletier E, Smith D, et al.
Comparison of hospitalisations and costs among bipolar patients who switched to extended-release quetiapine from immediate-release quetiapine.
Poster presented at 163rd Annual Meeting of the American Psychiatric Association, May 22-26th 2010, New Orleans, Louisiana, USA

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A strategy for preventing relapse

Medicines management

- Individualise treatment
- Engage patient by improving communication & information
- Ensure easy access to repeat prescription
- Ensure patient understands treatment regimen
- Align with daily routine
- Minimise complexity of treatment regimen

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Improving the use of medicines in severe mental illness

Medicines in Mental Health Ltd offers a range of services designed to obtain maximum benefit from medicines in the treatment of severe mental illness.

Thank you