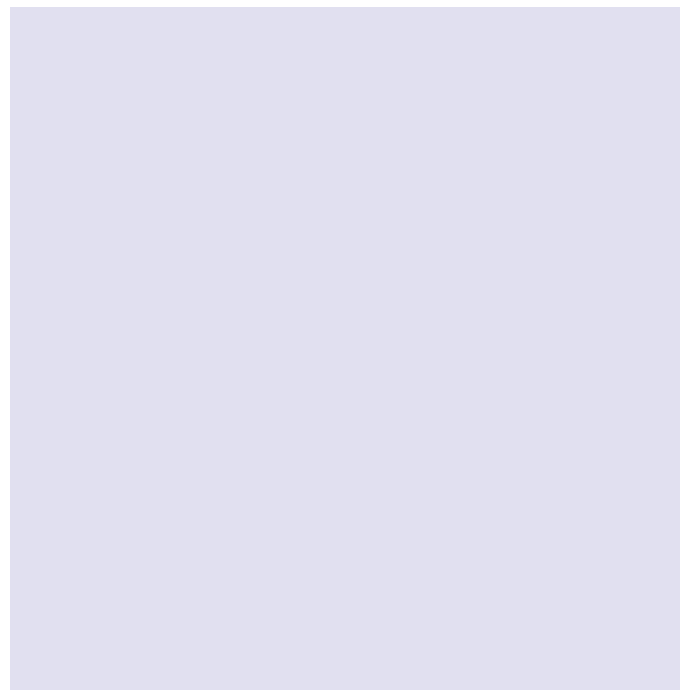


# BIPOLAR DISORDER

— aspects of drug treatment

By KAREN FRASER, MSc, MRPharmS, MORAG MARTIN, BSc, MRPharmS, ROBERT HUNTER, MD, MRCPsych, and STEVE HUDSON, MPharm, FRPharmS

*The aim of drug treatment in bipolar disorder is to manage acute episodes of mania, hypomania and depression and, in the longer term, prevent relapse. The second article in this month's special feature reviews the medicines available and sets out the pharmaceutical care issues that can improve patient compliance and, therefore, clinical outcomes*



CLIVE FREEMAN, THE ROYAL INSTITUTION/SPL

*A lithium atom: the loss of the outer electron (shown as the blue cloud) leads to the formation of the more stable lithium ion — still a mainstay in the prophylaxis of bipolar disorder*

There are two main aspects to the drug treatment of bipolar disorder — the short-term management of acute episodes of mania, hypomania and depression and long-term treatment to maximise the length of time between acute episodes. It is practical to consider the regimens used in acute episodes separately from those used for prophylaxis.

This article presents the currently available evidence for treating bipolar disorder. It is important to be aware that some studies demonstrate the efficacy of off-label or unli-

censed indications for drugs or preparations. Pharmacists and prescribers should make sure they know the limitations imposed by marketing authorisations (product licences) for individual products and seek expert advice where appropriate.

## TREATING ACUTE MANIA

Most patients with an acute manic episode will require treatment as a hospital inpatient. In an acute manic episode, the dose of any mood stabiliser should be optimised and treatment with an oral antipsychotic drug or valproic acid be initiated as appropriate. In patients with less severe forms of mania, monotherapy with the existing mood stabiliser may be possible. For patients not maintained on a mood stabiliser prior to admission, treatment with an oral antipsychotic drug or valproic acid is indicated. Some patients who are acutely unwell may require emergency treatment, following local protocols, with parenteral antipsychotics, benzodiazepines (usually lorazepam) or both. Oral benzodiazepines may also be of benefit in the short-term

treatment of acute mania where sedation is a priority, and their use might also reduce the dose of concurrent antipsychotic drugs required. Any drugs that could induce mania, such as antidepressants, should be reduced and discontinued during an acute manic episode.<sup>1</sup> Further information on the categories of drugs available to treat acute mania is set out below:

**Antipsychotics** Older, “typical” antipsychotic drugs have been used widely and appropriately for the treatment of symptoms associated with acute mania for some time. Although at least one notable review supporting their use exists,<sup>2</sup> there is generally a lack of high quality published evidence about their role.<sup>3</sup> Parenteral antipsychotics, used according to local protocols, are valuable for emergency situations in particularly agitated patients.<sup>4</sup>

Many of the “atypical” antipsychotic drugs have been studied in randomised controlled trials for acute mania. Olanzapine is currently licensed for this indication<sup>5-8</sup> and the National Institute for Clinical Excellence (NICE) has recently recommended

Ms Fraser is principal pharmacist for mental health, Ayrshire and Arran Acute Hospitals NHS Trust, Ms Martin is principal pharmacist for clinical services, Greater Glasgow Primary Care NHS Trust, Professor Hunter is consultant psychiatrist and director of research and development, Greater Glasgow Primary Care NHS Trust and honorary professor of psychiatry, University of Glasgow and Mr Hudson is Boots professor of pharmaceutical care, University of Strathclyde, Glasgow and Scottish Executive National Specialist in Pharmaceutical Care

that it should be considered as one of the treatment options in acute mania.<sup>9</sup> Similarly, quetiapine received a licence for acute mania after publication of the NICE guidance on newer treatments for mania and there is also clinical trial evidence to support its use for this indication.<sup>10,11</sup> Risperidone has demonstrated efficacy comparable with that of haloperidol in acute mania<sup>12</sup> but it is not as yet licensed in the UK for this indication.

In patients maintained on mood stabilising drugs who develop symptoms of mania, the mood stabiliser dose should be optimised before the antipsychotic drug is added as treatment.

**Anticonvulsant drugs** Studies have shown valproic acid (mainly as semisodium valproate) to be effective in treating acute mania.<sup>13,14</sup> Rapid dose titration is necessary for optimal antimanic effect.

Carbamazepine has also been studied, but it is not licensed for acute mania and is rarely used as a first line treatment.<sup>15</sup>

**Lithium** There is limited evidence to support the use of lithium as monotherapy in acute mania, although it may be a feasible option in less severe forms of mania for patients who are maintained on lithium as a prophylactic treatment.<sup>16</sup> (See “prophylactic drugs” below for further information about using lithium.)

**Benzodiazepines** Evidence supports the use of benzodiazepines (usually lorazepam in the UK) as adjunctive treatments, given parenterally if necessary, in patients with mania who are particularly agitated.<sup>4</sup>

## TREATING ACUTE DEPRESSION

**Antidepressants** At least one meta-analysis study supports the efficacy of antidepressants in treating episodes of depression in patients with bipolar disorder.<sup>17</sup> However, the evidence-base is limited, compared with the vast number of trials supporting the use of antidepressants in unipolar major depressive disorder.<sup>18</sup> As stated above, treatment with an antidepressant should be reduced and then withdrawn in patients who develop symptoms of acute mania.

**Lithium** There is limited evidence to support the efficacy of lithium in bipolar depression, despite its fairly widespread use in clinical practice for this indication.<sup>19</sup> (Further information about using lithium is contained in the “prophylactic drugs” section below.)

## PROPHYLACTIC DRUGS

It is generally advisable to start long-term treatment with mood stabilising drugs in patients who have had just a single severe

manic episode. This is because patient outcomes appear to improve if an early relapse is prevented.

The currently preferred strategy is to give continuous (rather than intermittent) maintenance treatment with a mood stabilising agent (with short-term treatments with antipsychotics and benzodiazepines being used at times of acute stress or if early symptoms of relapse are present.)

Lithium is generally considered to be the treatment of choice, with carbamazepine being seen as an alternative, particularly in bipolar II disorder or in patients for whom lithium is ineffective or unacceptable. Further information on these agents and others that are used to prevent relapse is set out below.

**Lithium** There is systematic review evidence to support the use of lithium as prophylactic treatment in bipolar disorder. For example, short-term and longer-term (up to three years) studies have shown that taking lithium reduces the likelihood of relapse. Lithium has been shown to be effective against both manic and depressive

relapse, but is more effective in manic relapse (and is therefore of most use in bipolar I disorder). It has been shown that treating patients who have bipolar disorder with lithium is specifically associated with a reduced risk of suicide. Treatment with lithium should not be suddenly withdrawn because this may lead to the development of mania.<sup>21</sup>

It should be noted that lithium preparations are not interchangeable — different brands may have widely varying bioavailabilities and so prescriptions should be written for a particular brand, rather than generically. In addition, lithium salts are not equivalent — ie, 200mg lithium carbonate is not equivalent to 200mg lithium citrate. These issues are particularly important, given the narrow therapeutic index of lithium. Patients receiving lithium should be issued with a “lithium card”. Side effects (which are usually dose-dependent) include gastrointestinal disturbance, weight gain, oedema, fine tremor, polyuria (increased frequency of urination), polydipsia (increased thirst) and hypothyroidism.

Further information on using lithium clinically (including dosing regimens, moni-

### Panel 1: Dosing regimens and monitoring requirements for patients being treated with lithium

#### Dosing regimens

- Camcolit (lithium carbonate). Treatment of manic episodes: 1.5–2.0g (elderly 0.5–1.0g) daily. Prophylaxis: 0.5–1.2g (elderly 0.5–1.0g) daily (as Camcolit250 in divided doses or Camcolit400 in single or divided doses)
- Liskonum (lithium carbonate). Treatment of manic episodes: 450–675mg (elderly 225mg) twice daily. Prophylaxis: 450mg (elderly 225mg) twice daily
- Priadel tablets (lithium carbonate). Treatment of manic episodes or prophylaxis: 400–1,200mg daily in single or divided doses (400mg twice daily in elderly and patients below 50kg).
- For Priadel liquid, Li-liquid and Litarex (lithium citrate), see manufacturers’ summaries of product characteristics for dosing information

#### Lithium monitoring

- Lithium blood levels should normally be measured on a three-monthly basis\* (for patients on established treatment)
- The blood sample should be taken at the same time interval post-dose on each occasion (ideally 12–18 hours)
- The following parameters should be checked annually:
  - Urea and electrolytes
  - Renal function (ie, serum creatinine/creatinine clearance; urine tested for presence of blood or protein)
  - Thyroid function
  - Weight, blood pressure and pulse
- Blood lithium levels of 0.4–1.0mmol/L are generally considered to be safe and effective

\*Certain patients (ie, elderly patients, those taking interacting medicines, and those with medical comorbidity, especially impaired renal, thyroid or cardiac function) may require more frequent monitoring. More frequent monitoring is also required if switching between lithium brands or between tablet and liquid formulations. It is also important to look out for signs of lithium toxicity — these include vomiting and severe diarrhoea, tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching, muscle weakness, lack of co-ordination, drowsiness or lethargy progressing to giddiness with ataxia, convulsions and electrocardiogram changes.

## Panel 2: Summary of key lithium drug interactions

Drugs implicated	Mechanism and effect
ACE inhibitors/ angiotensin-II antagonists	Exact mechanism of interaction unclear; lithium toxicity reported due to increase in lithium levels; renal toxicity may also occur.
Antacids	Sodium-containing antacids can cause increased lithium excretion leading to decrease in lithium levels and reduced effectiveness.
Antidepressants – SSRIs, MAOIs	SSRIs — neurotoxicity and increase in lithium levels; lithium toxicity and serotonin syndrome have been reported with certain SSRIs. MAOIs — increase in brain serotonin levels; serotonin syndrome reported with combination.
Antiepileptics	Carbamazepine — neurotoxicity reported in combination. Phenytoin — limited evidence of lithium toxicity.
Antipsychotics	CNS toxicity has been reported with a number of antipsychotics when given in combination with lithium.
Calcium channel blockers	Possible synergistic decrease in calcium ion transport, leading to neurotoxicity, worsening of mania, bradycardia.
Diuretics	Decreased lithium clearance leading to increased lithium concentrations and possible toxicity reported with thiazide (particularly), loop and potassium-sparing diuretics. Acetazolamide has, however, been reported to increase lithium excretion, leading to decreased levels and a loss of efficacy.
Methyldopa	Increased CNS response to lithium leading to increased risk of lithium toxicity/neurotoxicity.
Metronidazole	Increased lithium levels reported with combination; some reports of toxicity.
NSAIDs/ COX-II inhibitors	Decreased lithium clearance leading to increased lithium concentrations and possible toxicity. No such interaction reported with aspirin or sulindac.
Theophylline	Increased lithium clearance leading to reduction in lithium levels and reduced efficacy.

“SSRI” means selective serotonin reuptake inhibitor, “MAOI” means monoamine-oxidase inhibitor, “NSAID” means non-steroidal anti-inflammatory drugs, “COX-II” means cyclo-oxygenase-2 selective and “CNS” means central nervous system. This information is adapted from reference 24.

toring information, and drug interactions are set out in Panels 1 and 2).

**Carbamazepine** Evidence (from studies of between six weeks and three years duration) is emerging to support the use of carbamazepine as an alternative to lithium in preventing relapse.<sup>22,23</sup> Carbamazepine is licensed in the UK for prophylaxis of bipolar disorder.

**Valproic acid** Valproic acid compounds are also prescribed as maintenance treatments. This is an unlicensed indication, and the evidence base is limited compared with using lithium or carbamazepine — a single trial has demonstrated the efficacy of valproic acid (as valproate semisodium) in relapse preven-

tion of bipolar disorder compared with placebo.<sup>25</sup> Valproic acid appears to be more effective against depressive (rather than manic) relapse.

**Lamotrigine** Lamotrigine is licensed in the US (but not yet the UK) for maintenance treatment. There is increasing evidence of the benefit of lamotrigine in relapse prevention — trials have demonstrated relative benefit against depressive relapse compared with manic relapse.<sup>26,27</sup>

**Olanzapine** The atypical antipsychotic, olanzapine has recently been licensed in the UK for preventing relapse in patients with bipolar disorder whose manic episodes have responded to olanzapine treatment.

## SPECIAL POPULATIONS

In elderly patients, substantially lower doses of psychotropic drugs should be used at all stages in the management of bipolar disorder (see Panel 1 for indications of lithium dose in these patients).

Expert advice should also be sought before prescribing drugs for the treatment of bipolar disorder during pregnancy or lactation — there is a risk of teratogenicity from a number of the drugs used and only limited information is available about their use during breastfeeding (especially for lithium). Patients should be counselled about the “risk benefit” issues.

## CLINICAL GUIDELINES

There has been recent interest in producing guidelines for the management of bipolar disorder. In 2000 an expert panel in the US produced a consensus guideline,<sup>28</sup> and more recently evidence-based guidelines were developed by the British Association for Psychopharmacology.<sup>29</sup>

The Scottish Intercollegiate Guidelines Network (SIGN) is currently developing guidelines (which are likely to be published later on this year). In addition, NICE is due to publish guidance on bipolar disorder in 2006. This is positive news for health care professionals involved in the care of patients with bipolar disorder and, of course, for patients themselves. This is especially the case because bipolar disorder has been recognised as a condition that has been relatively neglected in the past.<sup>29</sup>

## INDIVIDUAL PATIENT CARE

One key aspect to individual patient care is teaching patients to recognise the early symptoms of manic relapse and seek early treatment. This is important because it is associated with preventing relapse and improving the social functioning and employment prospects of patients.<sup>30</sup>

Improving compliance is another aspect of individualised care. Compliance issues are particularly associated with the prophylactic use of lithium. Lithium treatment can cause unwanted effects (see above) and patients may see it as bringing a negative influence on their behaviour, personality or life-style. Regular three-monthly monitoring of lithium blood concentrations is also required (see Panel 1).

Lithium clinics are useful in improving patient compliance and concordance and therefore clinical outcomes.<sup>31,32</sup> Community pharmacists also have an important role to play in achieving compliance through monitoring their patients and educating them about the drug. Panel 3 (p143) summarises the pharmaceutical care issues associated with the treatment of patients with bipolar disorder.

### Panel 3: Pharmaceutical care issues in treating patients with bipolar disorder

Stage of treatment	Actions	Points to consider
<p>Development of a treatment plan:</p> <ul style="list-style-type: none"> <li>● Patient comprehension</li> <li>● Active participation</li> <li>● Patient's characteristics</li> <li>● Indication (the need for each drug)</li> <li>● Drug history</li> <li>● Choice of medicines</li> <li>● Contraindication/ interaction</li> <li>● Conformity to guidelines</li> <li>● Continuity of care</li> </ul>	<p>Verify the plan in respect of:</p> <ul style="list-style-type: none"> <li>● Patient's characteristics</li> <li>● Suitability of medicines</li> <li>● Patient's needs for education</li> <li>● Concordance and agreed expectations</li> </ul> <p>Modify the plan to address:</p> <ul style="list-style-type: none"> <li>● Specific educational needs</li> <li>● Need for individualisation of treatment plan</li> </ul>	<ul style="list-style-type: none"> <li>● Identifying concomitant physical disorders that are associated with or which complicate the mood disorder</li> <li>● Identifying relevant social circumstances, family environment, family stigma and support</li> <li>● Alerting the patient to common side effects of medication and provide reassurance</li> <li>● Verifying an accurate drug history, including any prior use of antidepressants and other psychoactive agents and over-the-counter (OTC) products</li> <li>● Identifying other medication that can cause or aggravate mood disorders</li> <li>● Identifying co-morbid states that complicate treatment and its evaluation(eg, thyroid disorders)</li> <li>● Collaborating with other team members to establish alertness to risk of overdose</li> <li>● Providing advice on request about patient support groups</li> </ul>
<p>Implementation of the treatment plan:</p> <ul style="list-style-type: none"> <li>● Dose</li> <li>● Frequency</li> <li>● Timing</li> <li>● Compliance</li> <li>● Clinical signs</li> <li>● Laboratory markers</li> </ul>	<p>Monitor the patient for:</p> <ul style="list-style-type: none"> <li>● Continuing suitability of drug/dose regimen</li> <li>● Signs/symptoms of effectiveness and toxicity</li> </ul> <p>Adjust the process by:</p> <ul style="list-style-type: none"> <li>● Further individualisation in response to monitoring</li> </ul>	<ul style="list-style-type: none"> <li>● Including the patient in self monitoring and good documentation of symptoms where the disease has an irregular course</li> <li>● Ensuring dose individualisation using information and preferences from patients</li> <li>● Securing support and information from relatives and friends to allow them to supervise medication and report on symptoms when the patient is ill</li> <li>● Being similarly alert to the possibility of patients receiving misconceptions about the disease and its treatment from others</li> <li>● Checking compliance and maintenance of concordance. Written treatment contracts may support implementation of treatment</li> <li>● Checking the handling of medicines and safety of storage</li> <li>● Specific monitoring of renal function for lithium in conjunction with therapeutic drug monitoring</li> <li>● Watching for specific drug-induced syndromes such as syndrome of inappropriate antidiuretic hormone secretion</li> <li>● Checking for specific drug interactions, including those with OTC products</li> </ul>
<p>Clinical outcome:</p> <ul style="list-style-type: none"> <li>● Therapeutic benefit</li> <li>● Safety</li> <li>● Unwanted symptoms</li> <li>● Recorded adverse drug reaction</li> </ul>	<p>Confirm evidence of treatment success:</p> <ul style="list-style-type: none"> <li>● Reassure patient in relation to agreed expectations</li> </ul> <p>Prompt a review from:</p> <ul style="list-style-type: none"> <li>● Identification of treatment failure</li> <li>● Newly identified patient's needs</li> <li>● Sharing information and discussion of implications with the prescriber and other team members</li> </ul>	<ul style="list-style-type: none"> <li>● Acknowledging adverse effects as perceived by patients</li> <li>● Recognising persistent side effects requiring clinical review of the therapeutic plan</li> <li>● Confirming adequate duration of acute treatment course</li> <li>● Recognising symptomatic changes to allow early referral for a clinical review of the patient's needs</li> </ul>

## SUMMARY

Progress in treating patients with bipolar disorder continues to be made. Relatively recent developments include the use of atypical antipsychotic drugs to control manic episodes and as maintenance therapy.

In addition, SIGN guidelines are expected at the end of the year and NICE guidelines are due out in 2006. These developments will be particularly welcome given that bipolar illness has been a relatively neglected condition to date. A greater understanding of the neurobiology involved should further aid the development of new drugs.

## REFERENCES

1. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Washington DC: American Psychiatric Association; 1994.
2. Cookson J. Use of antipsychotic drugs and lithium in mania. *British Journal of Psychiatry* 2001;41(Suppl):S148–56.
3. Johnstone EC, Crow TJ, Frith CD, Owens DG. The Northwick Park “Functional” Psychosis Study: diagnosis and treatment response. *Lancet* 1988;2:119–25.
4. Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP. Expert consensus panel for behavioural emergencies. The expert consensus guideline series. Treatment of behavioral emergencies. *Postgraduate Medicine* 2001;Spec No;1–88.
5. Summary of Product Characteristics: Zyprexa. Available from [www.medicines.org.uk](http://www.medicines.org.uk) (accessed 15 March 2004).
6. Summary of Product Characteristics: Seroquel. Available from [www.medicines.org.uk](http://www.medicines.org.uk) (accessed 15 March 2004).
7. Rendell JM, Gijssman HJ, Keck P, Goodwin GM, Geddes JR. Olanzapine alone or in combination in acute mania. *Cochrane Library* 2004; issue 1.
8. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, et al. Efficacy of olanzapine in acute bipolar mania: A double-blind, placebo-controlled study. *Archives of General Psychiatry* 2000;57:841–9.
9. National Institute for Clinical Excellence. Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London: NICE 2003.
10. Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E. Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12 month open-label study. *Journal of Affective Disorder* 2003;76:267–71.

11. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;41:1216-23.
12. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: A double-blind, placebo-controlled comparison of efficacy and safety. *American Journal of Psychiatry* 2002; 157: 1146-54.
13. Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. *Cochrane Library* 2004; issue 1.
14. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. Double blind comparison of valproate and lithium in the treatment of acute mania. *American Journal of Psychiatry* 1992;149:108-11.
15. Okomu T, Kishimoto A. A history of investigation on the mood stabilizing effect of carbamazepine in Japan. *Psychiatry and Clinical Neurosciences* 1998;52:3-12.
16. Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatrica Scandinavica* 1999;100: 406-17.
17. Anderson IM, Nutt DJ, Deakin JF. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology Guidelines. *Journal of Psychopharmacology* 2000; 14:3-20.
18. Storosum JG, Elferink AJ, van Zwieten BJ, van den Brink W, Gersons BP, van Strik R, et al. Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic study. *European Neuropsychopharmacology* 2001; 11:173-80.
19. Bhagwager Z, Goodwin GM. The role of lithium in the treatment of bipolar depression. *Clinical Neuroscience Research* 2002;2:22-227.
20. Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *Cochrane Library* 2004; issue 1.
21. Mander AJ and Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; 2: 15-7.
22. Placidi GF, Lenzi A, Lazzarini F, Cassano GB, Akiskal HS. The comparative efficacy and safety of carbamazepine versus lithium: A randomized, double-blind 3 year trial in 83 patients. *Journal of Clinical Psychiatry* 1986;47: 490-94.

This list of references is abridged. A full list is available on the next page

## REFERENCES

1. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Washington DC: American Psychiatric Association; 1994.
2. Cookson J. Use of antipsychotic drugs and lithium in mania. *British Journal of Psychiatry* 2001;41(Suppl):S148–56.
3. Johnstone EC, Crow TJ, Frith CD, Owens DG. The Northwick Park “Functional” Psychosis Study: diagnosis and treatment response. *Lancet* 1988;2:119–25.
4. Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP. Expert consensus panel for behavioural emergencies. The expert consensus guideline series. Treatment of behavioral emergencies. *Postgraduate Medicine* 2001;Spec No;1–88.
5. Summary of Product Characteristics: Zyprexa. Available from [www.medicines.org.uk](http://www.medicines.org.uk) (accessed 15 March 2004).
6. Summary of Product Characteristics: Seroquel. Available from [www.medicines.org.uk](http://www.medicines.org.uk) (accessed 15 March 2004).
7. Rendell JM, Gijsman HJ, Keck P, Goodwin GM, Geddes JR. Olanzapine alone or in combination in acute mania. *Cochrane Library* 2004; issue 1.
8. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, et al. Efficacy of olanzapine in acute bipolar mania: A double-blind, placebo-controlled study. *Archives of General Psychiatry* 2000;57:841–9.
9. National Institute for Clinical Excellence. Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London: NICE 2003.
10. Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E. Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12 month open-label study. *Journal of Affective Disorder* 2003;76:267–71.
11. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;41:1216–23.
12. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: A double-blind, placebo-controlled comparison of efficacy and safety. *American Journal of Psychiatry* 2002; 157: 1146–54.
13. Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. *Cochrane Library* 2004; issue 1.
14. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. Double blind comparison of valproate and lithium in the treatment of acute mania. *American Journal of Psychiatry* 1992;149:108–11.
15. Okomu T, Kishimoto A. A history of investigation on the mood stabilizing effect of carbamazepine in Japan. *Psychiatry and Clinical Neurosciences* 1998;52:3–12.
16. Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatrica Scandinavica* 1999;100: 406–17.
17. Anderson IM, Nutt DJ, Deakin JF. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology Guidelines. *Journal of Psychopharmacology* 2000; 14:3–20.
18. Storosum JG, Elferink AJ, van Zwieten BJ van den Brink W, Gersons BP, van Strik R, et al. Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic study. *European Neuropsychopharmacology* 2001; 11:173–80.
19. Bhagwager Z, Goodwin GM. The role of lithium in the treatment of bipolar depression. *Clinical Neuroscience Research* 2002;2:22–27.
20. Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *Cochrane Library* 2004; issue 1.
21. Mander AJ and Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; 2: 15–7.
22. Placidi GF, Lenzi A, Lazzarini F, Cassano GB, Akiskal HS. The comparative efficacy and safety of carbamazepine versus lithium: A randomized, double-blind 3 year trial in 83 patients. *Journal of Clinical Psychiatry* 1986;47: 490–94.
23. Luszkat RM, Murphy DP, Nunn CM. Carbamazepine vs lithium in the treatment and prophylaxis of mania. *British Journal of Psychiatry* 1988;153: 198–204.
24. Fraser K, Martin M, Hunter R, Hudson S. Mood disorders: Bipolar conditions. *The Pharmaceutical Journal* 2001;266: 824–32.
25. Macritchie KA, Geddes JR, Scott J, Haslam DR, Goodwin GM. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. *Cochrane Library* 2004; issue 1.
26. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *Journal of Clinical Psychiatry* 1999;60:79–88.
27. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP et al. Lamictal 605 study group. 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.
28. Sachs GS, Prinz DJ, Kahn DA, Carpenter D, Docherty JP. Expert consensus guideline series: Medication treatment of bipolar disorder. *Postgraduate Medicine* 2000;Spec No:1–104.
29. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2003;17: 149–73.
30. Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *British Medical Journal* 1999;318: 149–53.
31. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness: efficacy, effectiveness and efficiency. *British Journal of Psychiatry* 1994;164: 741–46.
32. Maj M, Pirozzi R, Magliano L. Long-term outcome of lithium prophylaxis in bipolar disorder: A 5-year prospective study of 402 patients at a lithium clinic. *American Journal of Psychiatry* 1998;155:30–5.