

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder¹

1 Guidance

- 1.1 Olanzapine and valproate semisodium, within their licensed indications, are recommended as options for control of the acute symptoms associated with the manic phase of bipolar I disorder.
- 1.2 Of the drugs available for the treatment of acute mania, the choice of which to prescribe should be made jointly by the individual and the clinician(s) responsible for treatment. The choice should be based on an informed discussion of the relative benefits and side-effect profiles of each drug, and should take into account the needs of the individual and the particular clinical situation.
- 1.3 In all situations where informed discussion is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted when appropriate.

2 Clinical need and practice

- 2.1 Bipolar disorder is a chronic psychiatric illness characterised by alternating episodes of mania (or hypomania) and depression. Clinical guidelines and

¹ At the date of issue of this guidance, within the classes of agents referred to the Institute by the Department of Health and the Welsh Assembly Government only olanzapine and valproate semisodium held a marketing authorisation for the treatment of acute mania in bipolar I disorder.

trials commonly classify bipolar disorder according to definitions in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). There are two principal types of bipolar disorder: bipolar I and bipolar II. In bipolar I disorder, the essential feature is a clinical course characterised by the occurrence of manic or mixed episodes, where the manic episodes are severe and cause marked impairment in functioning, frequently resulting in hospitalisation. In bipolar II disorder, individuals do not meet the criteria for full mania and are described as hypomanic. Hypomania is distinguished from mania by the absence of psychotic symptoms and less impaired functioning; individuals with hypomania do not normally require hospitalisation. This guidance only considers the management of acute mania associated with bipolar I disorder.

- 2.2 Mania is diagnosed by the concurrent presence of at least three of the following symptoms: grandiosity/inflated self-esteem, decreased need for sleep, talkativeness (pressured speech), flight of ideas (rapidly racing thoughts and flitting of ideas), marked distractibility, increased goal-directed activity/psychomotor agitation, excessive involvement in pleasurable activities without regard for negative consequences (for example buying sprees, sexual indiscretions, foolish business ventures). Many people with bipolar disorder also experience psychotic symptoms such as delusions and hallucinations.
- 2.3 A manic episode may also be described as 'mixed', when depressive symptoms occur in the context of manic behaviours and thinking. Depressive symptoms and symptoms of mania (or hypomania) may alternate from day to day, or even hour to hour.
- 2.4 The frequency and duration of episodes and asymptomatic periods are variable, although remissions tend to get shorter over time. Manic episodes last for between 2 weeks and 4–5 months. Depressive episodes are longer, with a median duration of about 6 months. Some individuals experience an

episode of mania that quickly switches into depression, often as an indirect result of treatment used to manage the acute manic condition. A subgroup of approximately 10–20% of individuals with bipolar disorder experiences 'rapid cycling', characterised by four or more cycles of depression and mania a year, with no intervening asymptomatic periods. A rapid cycling pattern may be associated with a poorer prognosis.

- 2.5 Bipolar disorder (I and II) has a point prevalence of 1.3% in the general adult population, suggesting that 546,000 individuals over the age of 15 years are affected in England and Wales. Bipolar I disorder affects men and women almost equally, but there is a higher prevalence of hypomanic episodes (bipolar II) among women.
- 2.6 Between episodes, people with bipolar disorder may be well enough to work and have a normal lifestyle, but bipolar disorder often has profound adverse consequences on an individual's quality of life, including personal relationships and social functioning. In addition to the immediate effects of acute mania, for example dehydration, exhaustion and lack of self-care, any inappropriate actions may lead to financial difficulties and loss of employment. The behavioural manifestations of acute mania also cause difficulties with drug treatment, as individuals may be reluctant to take any medication that blunts the heightened mood associated with mania.
- 2.7 Estimates of lifetime suicide risk in individuals with bipolar disorder range from 15% to 19%, with an estimated third of individuals with bipolar disorder having made a suicide attempt. Suicide occurs more often among men than women, and is most likely during a depressive episode. Individuals with bipolar disorder commonly have co-morbid psychiatric disorders, or misuse drugs or alcohol.
- 2.8 The management of bipolar I disorder is complex and depends on the phase of the disorder being experienced (that is, acute mania, depression, or maintenance to prevent further episodes). In March 2003, the Institute was

asked by the Department of Health and Welsh Assembly Government to produce guidelines on the management of bipolar disorder, but publication is not expected before 2006.

- 2.9 Some of the drugs used in the management of bipolar I disorder act as both an antimanic agent and a prophylactic agent to prevent relapses. Drugs that are used to treat the manic phase are commonly continued during remission, with the aim of preventing or delaying another relapse. Many agents are used outside their licensed indications, and therapies are often used in combination. Adjunctive use of antipsychotics and benzodiazepines is common.
- 2.10 Lithium salts (carbonate and citrate) have historically been the mainstay of treatment and are licensed for the treatment and prophylaxis of mania, 'manic-depressive illness' and recurrent depression. However, lithium is associated with a number of unpleasant and potentially fatal side effects and the plasma levels required for therapeutic effect are very close to those at which toxicity occurs. This makes dose adjustment difficult, and frequent monitoring is required. The anticonvulsants sodium valproate and carbamazepine are used in clinical practice both as alternatives and adjuncts to lithium. However, sodium valproate does not have a UK licence for the treatment of bipolar disorder, and carbamazepine is licensed only for the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium.
- 2.11 There are several different strategies for the management of acute mania and there is no consensus about which is the most appropriate. Prophylactic agents can be initiated singly or in combination, and may be used concurrently with an agent to control the acute symptoms of mania (for example, an antipsychotic or valproate semisodium [VSS]). An alternative strategy is to start the prophylactic agent once the patient's mood has been stabilised by an antimanic drug. Benzodiazepines are also often used in the

initial stages of treatment of acute mania. Although treatment with the antimanic drug may be withdrawn as the prophylactic agent becomes effective, audits have revealed that many individuals remain on antimanic drugs, particularly antipsychotics, for extended periods.

- 2.12 Antipsychotics can be broadly subdivided into two classes: the older 'typical' agents (neuroleptics), for example haloperidol and chlorpromazine; and the newer 'atypical' agents such as olanzapine. All antipsychotic agents are associated with side effects, but the profile and clinical significance of these differs among individuals and drugs. Side effects may include extrapyramidal symptoms (such as parkinsonism, acute dystonic reactions, akathisia and tardive dyskinesia), autonomic effects (such as blurring of vision, increased intraocular pressure, dry mouth and eyes, constipation and urinary retention), increased prolactin levels, seizures, sedation, cardiac electrical instability and weight gain. Of particular concern is tardive dyskinesia (involuntary orofacial and trunk movements), which may not be evident immediately, and which may be irreversible and may worsen on treatment withdrawal. Although the incidence of side effects is related to the administered dose, atypical antipsychotics in general are associated with a reduced incidence of extrapyramidal symptoms compared with typicals.

3 The technologies

- 3.1 The Department of Health and the Welsh Assembly Government asked the Institute "to advise on the clinical and cost effectiveness of any medicines in the class of atypical antipsychotics or anticonvulsants which are or may imminently be licensed for treatment of bipolar disorder, in comparison with best current practice including lithium". There are no drugs within either of these two classes that currently hold a marketing authorisation for either prophylaxis of acute mood episodes or for the management of acute depression associated with bipolar disorder. At the date of issue of this guidance, within the classes of agents referred to

the Institute by the Department of Health and the Welsh Assembly Government, only olanzapine and VSS held a marketing authorisation for the management of acute mania in bipolar I disorder.

3.2 Olanzapine

- 3.2.1 Olanzapine is licensed for the treatment of moderate to severe manic episodes. The recommended dose in combination therapy is 10 mg daily, adjusted to a usual range of 5–20 mg daily (doses greater than 10 mg daily only after reassessment). In monotherapy, the recommended dose is 15 mg daily, adjusted to a usual range of 5–20 mg daily (doses greater than 15 mg only after reassessment). There is no recommended dose adjustment for older people, and olanzapine is not recommended for people under 18 years of age.
- 3.2.2 The Summary of Product Characteristics states that weight gain and somnolence are very common side effects of olanzapine. Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases, and therefore appropriate clinical monitoring is advisable in people with diabetes or with risk factors for the development of diabetes mellitus. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.2.3 Olanzapine is also licensed as an intramuscular (IM) injection for use in rapid control of agitation and disturbed behaviours in individuals with a manic episode when oral therapy is not appropriate.
- 3.2.4 The listed costs of 28 olanzapine tablets are (excluding VAT; *British National Formulary* 45, March 2003): 2.5 mg £31.70; 5 mg £48.78; 10 mg £97.56; and 15 mg £146.34. The 7.5-mg tablets cost £146.34 for 56. Costs may vary in different settings because of negotiated procurement discounts. There is currently no price available for IM olanzapine.

3.3 Valproate semisodium

- 3.3.1 VSS is an equimolar combination of sodium valproate and valproic acid. It is licensed for the acute treatment of a manic episode associated with bipolar disorder. The recommended dose of VSS is initially 750 mg daily in two or three divided doses, increased according to response, with a usual dose of 1–2 g daily. There are no recommended dose reductions for older people. The Summary of Product Characteristics states that the safety and efficacy of VSS have not been studied in people under the age of 18 years and therefore the *British National Formulary* does not recommend its use in this patient group.
- 3.3.2 Pharmacokinetic data submitted to the Institute by the manufacturer, Sanofi Synthelabo, indicated that the mean time to peak plasma concentration is 213 minutes for VSS compared with 246 minutes for modified-release sodium valproate.
- 3.3.3 The Summary of Product Characteristics states that VSS very commonly causes weight gain, which may be marked and progressive. Severe, sometimes fatal, liver damage has exceptionally been reported. Liver function should be assessed before therapy and during the first 6 months; tests that reflect protein synthesis, particularly prothrombin time, are most relevant. Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are therefore recommended. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.3.4 The listed costs of 90 VSS tablets (excluding VAT; *British National Formulary* 45, March 2003) are: 250 mg £43.19; 500 mg £72.19. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 *Clinical effectiveness*

Monotherapy

4.1.1 Olanzapine

4.1.1.1 Evidence from six randomised controlled trials (RCTs) was examined that compared oral olanzapine monotherapy with placebo (two RCTs), haloperidol (one RCT), lithium (one RCT) and VSS (two RCTs). The evidence from post hoc analyses showed that olanzapine was more effective than placebo up to 4 weeks, and at 6 weeks the effects of olanzapine were similar to those of haloperidol. The lithium versus olanzapine trial suggested that the outcomes at 4 weeks may be similar for the two drugs, although only very limited data were available and the trial contained too few patients (30) to state equivalence. Over a 24-hour period, IM olanzapine was shown to control severe agitation to a similar degree to IM lorazepam in a placebo-controlled RCT that enrolled 201 patients. The studies comparing olanzapine with VSS are discussed in Section 4.1.3.

4.1.2 Valproate semisodium

4.1.2.1 Evidence from three RCTs demonstrated that VSS was more effective than placebo and produced similar outcomes to lithium in the management of acute mania. A fourth RCT demonstrated that VSS was more effective than placebo at 1–3 weeks in 43 patients who were resistant or intolerant to lithium. A fifth RCT found no statistically significant differences between VSS and haloperidol after 6 days' treatment, although the study was too small (42 patients) to establish equivalence, and at 6 days all enrolled patients still had manic symptoms as assessed by the Young Mania Rating Scale (YMRS) with all scores greater than 14 which is the minimum used in most RCTs to define mania. Two studies comparing olanzapine with VSS are discussed in Section 4.1.3.

4.1.3 Head-to-head evidence

4.1.3.1 Two RCTs were reviewed that compared olanzapine with VSS in patients with acute mania, including rapid cycling disorder. There were no statistically significant differences in any outcome except that mean change in the YMRS in the larger study at 3 weeks (mean difference [MD] 3.0; 95% confidence interval [CI], 0.62 to 5.38) was in favour of olanzapine. Subgroup analysis indicated that this may be due to greater improvement with olanzapine in the 50% of enrolled patients who were not psychotic (MD 5.4; 95% CI, 2.53 to 8.27; statistical test for interaction, $p = 0.061$). Olanzapine was associated with a greater risk of dry mouth, somnolence, speech disorder, increased appetite and weight gain; VSS was associated with a greater incidence of gastrointestinal adverse events. Whilst there were no significant differences between the treatments for change scores on the Abnormal Involuntary Movement Scale or the Barnes Akathisia Scale, the Simpson Angus Scale change score was in favour of VSS (MD 0.72; 95% CI, -1.33 to -0.11).

4.1.4 Summary

4.1.4.1 The evidence from placebo-controlled RCTs supports the use of olanzapine and VSS as monotherapy for the management of acute mania in patients with bipolar I disorder. Although evidence from RCTs was available, it could not be conclusively determined whether olanzapine or VSS had an antimanic action better than, worse than, or equivalent to any of the more established therapies. Although in some trials some of the outcome measures suggested a difference, the data were not consistent. There is evidence to suggest that individual subgroups of patients may benefit more from certain interventions, but the evidence is not robust. Olanzapine may be of greater benefit than VSS in individuals without psychosis, and one very small study (43 patients) indicated that VSS monotherapy might be effective in individuals who are either intolerant or resistant to lithium.

However, the differing treatment durations (1–3 weeks) mean that this cannot be conclusively stated.

Adjunctive therapy

4.1.5 Olanzapine

4.1.5.1 A 6-week RCT was identified that examined adjunctive use of olanzapine in individuals with an inadequate response to at least 2 weeks of monotherapy with either lithium or VSS. At 42 days, a greater proportion of patients (149/229 compared with 51/115) who received adjunctive olanzapine combination had a 50% reduction in YMRS (relative risk 1.47; 95% CI, 1.17 to 1.84) compared with those who received adjunctive placebo. The results from this study show that in individuals who are not responding to monotherapy with either lithium or VSS, the addition of olanzapine may be of benefit, although more side effects are experienced. The results of this study cannot be generalised to all patients, because only those who did not respond to initial single-agent therapy were included and there is no evidence whether they would have also responded to a switch to olanzapine as a monotherapy.

4.1.6 Valproate semisodium

4.1.6.1 No RCTs were identified.

4.2 Cost effectiveness

4.2.1 Olanzapine

4.2.1.1 The literature review did not find any studies evaluating the cost effectiveness of olanzapine.

4.2.1.2 The manufacturer's submission presented a modification of a US model published by Keck et al. in 1996. Costs and symptom-free days over 1 year were calculated according to the different episode types. The authors

concluded that olanzapine monotherapy resulted in similar costs and outcomes to VSS, but was more effective and cheaper than haloperidol. Reductions in cost were driven mainly by a reduction in inpatient costs for each of the patient subtypes included in the model.

4.2.2 Valproate semisodium

- 4.2.2.1 A literature review found one published economic model from the USA (Keck et al. 1996) that compared lithium with VSS given by a rapid oral loading strategy in patients initially admitted to hospital with acute mania and treated for a period of 1 year. Effectiveness parameters for the model were derived from the literature and the University of Cincinnati Mania Project Database. In the base case, VSS was superior to lithium in terms of response rate at 3 weeks (0.59 vs 0.49) and decreased length of initial hospitalisation (14 vs 18 days). Relapse after the initial period was assumed to be equivalent in both treatment groups. Mean total costs of the different treatment strategies over the year were estimated as US\$43,400 for lithium and US\$39,643 for VSS.
- 4.2.2.2 The manufacturer's submission presented a version of the model by Keck et al., modified to reflect UK costs and practice. All patients were hospitalised for acute mania at the start of the model. Length of hospital stay was estimated by applying the ratio of the difference seen in US studies to UK length-of-stay data (33 days for lithium vs 26 days for VSS). In the base case, with response at 3 weeks assumed to be the same as in the US model, VSS cost £7223 over the 1 year compared with £8090 for lithium. When response rates are assumed to be equivalent, VSS is still cheaper than lithium, largely as a result of favourable assumptions of a shorter length of hospital stay.

4.2.3 The Assessment Group model

4.2.3.1 The model assessed the cost effectiveness of lithium, haloperidol, olanzapine and VSS given as monotherapy for the treatment of an acute manic episode in patients with bipolar I disorder. The effectiveness outcome was a response rate at 3 weeks, based on a 50% or greater improvement in mania rating scale scores. Estimates of response to each of the treatments were obtained by synthesising the data from RCTs using health economic modelling techniques (a hierarchical Bayesian model simulated using a Markov chain Monte Carlo technique). As modelled, the mean (and 95% CIs) response estimates for all treatments were very similar: olanzapine 0.54 (95% CI, 0.46 to 0.62) and VSS 0.45 (95% CI, 0.37 to 0.54). Mean response rates for haloperidol and lithium were between those for olanzapine and VSS but cannot be reported in full because they were calculated in part from data submitted as commercial in confidence.

4.2.3.2 The base case assumed there were no differences in initial hospitalisation rates. Based on an incremental comparison of mean response rates and costs, the cost-effectiveness results showed that haloperidol was more effective and cheaper than lithium and VSS. Olanzapine is more expensive than haloperidol and on the central estimate it is more effective, although this is not a statistically significant difference. The model's best estimate suggests that the use of olanzapine rather than haloperidol would be associated with an additional cost of £7165 for every additional responder. This result was not sensitive to the additional cost of treating extrapyramidal symptoms, which are an important side effect of haloperidol. The uncertainty surrounding these estimates was presented in the form of cost-effectiveness acceptability curves.

4.3 Other evidence

4.3.1 The evidence from the patient groups highlighted deficiencies in the care of individuals with acute mania. Of particular concern was the fact that

admission to hospital was dependent on the availability of acute facilities. This led to local variations in policy. As a result, individuals with acute mania were often cared for at home, increasing the burden on carers. This burden was further increased because individuals with acute mania often did not recognise their symptoms and were unwilling to accept care, which led to delays in treatment.

- 4.3.2 The patient groups emphasised that patients were often prescribed inappropriate doses, and did not receive sufficient monitoring, which could increase side effects, particularly with respect to typical antipsychotics. Concern was expressed about the validity of rating scales commonly used in clinical trials, because the scales did not capture side effects, and about the fact that some individuals learned to mask their symptoms during assessment periods. The priority was therefore for a medication that had a rapid onset of action and had few accompanying side effects.

4.4 *Consideration of the evidence*

- 4.4.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of olanzapine and VSS to treat acute mania associated with bipolar I disorder, having considered evidence on the nature of the condition and the value placed by users on the benefits of these technologies from people with bipolar disorder, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.
- 4.4.2 Overall, the Committee considered that the available RCT evidence supported the efficacy (in terms of control of acute symptoms) of olanzapine and VSS when used as monotherapy in the management of acute mania. However, although it appreciated the difficulties in conducting trials in individuals with bipolar I disorder, it did not consider that the available evidence was sufficiently robust to allow a distinction to be made between the two drugs, or to recommend one drug over another on efficacy grounds.

This was true for the comparisons between olanzapine and VSS, and for the comparisons between the appraised drugs and alternatives such as lithium, sodium valproate and the typical antipsychotics.

4.4.3 The Committee noted the important differences in the contraindications and side-effect profiles of the individual agents used in the management of acute mania. The Committee also appreciated that tolerance of specific side effects differs greatly between individuals, and that experience of adverse events early on in the disease history may affect individuals' future concordance with their medication. Thus, the Committee considered that, in the absence of definitive evidence of superiority in clinical or cost effectiveness, the choice of the most appropriate treatment regimen would usually depend on the clinical situation, individual circumstances, and the patient's preference. The Committee therefore concluded that in addition to existing, more established treatments for acute mania, olanzapine and VSS should be recommended as options for treatment.

4.4.4 The Committee expressed particular concern that much of the RCT evidence reviewed might not reflect clinical practice, and about the overall lack of evidence to support current management strategies. In particular, it was noted that there was substantial use of drugs outside their current licensed indications, which prevented the Committee from addressing their use. It was evident that, despite the lack of RCT evidence, olanzapine and VSS were commonly used in combination therapy. This may be a result of the perceived need to continue previously prescribed maintenance therapy for an individual experiencing their second or subsequent episode of acute mania or to provide treatment for an individual who does not initially respond to monotherapy. On this basis, the Committee did not consider it would be appropriate to make any recommendation against combination therapy, and considered it imperative that appropriate studies should be set up to investigate this combined use.

- 4.4.5 The Committee heard expert testimony that many people with acute mania were continued on medications they received during the acute phase for weeks or months after symptom control had been achieved. This practice was not based on substantive evidence, and was of unproven cost effectiveness. The Committee was advised that clinicians were reluctant to remove individuals from medications that had initially stabilised the acute episode.
- 4.4.6 Experts also indicated that effective medication was likely to reduce suicide attempts and completed suicides, but no definitive data were presented. The Committee considered that an effect on both attempted and completed suicides could be an important factor in defining the most appropriate drug regimens for bipolar I disorder, and that further research to define this effect was important.
- 4.4.7 The Committee took account of the high costs associated with hospitalisation of individuals suffering an episode of acute mania, and the relatively small proportion of these total costs that related to drug therapy and monitoring. Thus any reduction in either the rates of hospitalisation or the length of hospital stay resulting from the use of individual drugs would be the key factor in determining overall cost effectiveness. It was therefore thought most likely that both of the drugs considered would be cost effective when compared with no treatment, and of similar cost effectiveness to each other when there was good patient adherence to treatment. The Committee did not, however, consider the evidence sufficiently reliable to determine whether any particular drug used in the treatment of mania resulted in a decrease in hospitalisation or length of hospital stay relative to any other drug.
- 4.4.8 In conclusion, the Committee considered that because it was not possible to distinguish between the efficacy of olanzapine and VSS on the basis of response rates or length of hospitalisation, and because the total costs were

likely to be similar, no distinction could be made between olanzapine and VSS and any of the other treatments for acute mania in terms of their relative cost effectiveness. The Committee concluded that the incremental cost-effectiveness ratios presented in the Assessment Report were not likely to be robust because of the uncertainties in the analysis and restrictions imposed by the lack of available data and the design of trials. The Committee was persuaded that the appropriate use of olanzapine or VSS in the management of acute mania was likely to be cost effective. Given the limitations of the available data and the fact that olanzapine and VSS are not licensed for prophylaxis, the Committee did not consider it appropriate to make recommendations on these agents beyond their use for control of the acute symptoms associated with the manic phase of bipolar I disorder. The Committee also emphasised that, although this appraisal did not examine the cost effectiveness of long-term use, such long-term use was likely to substantially affect the relative cost effectiveness of the drugs.

5 Recommendations for further research

- 5.1 Further RCTs, of adequate design, of olanzapine and VSS against more established antimanic agents are urgently needed. These should consider both monotherapy and combination therapies and, to inform clinical practice, data should be collected on how long these agents should be continued.
- 5.2 There is preliminary evidence to suggest that individual subgroups of patients (for example those with psychosis or rapid cycling disease) may respond differently to a given intervention. Further research is needed; population subgroups should be identified before any data collection, and trials should be designed appropriately to take account of subgroup responses to treatment.
- 5.3 Cohort studies are needed to establish any differences in longer-term morbidity or mortality (particularly attempted and completed suicides) associated with all interventions for the management of acute mania.

6 Implications for the NHS

- 6.1 The overall costs (including hospitalisation and therapeutic monitoring) of olanzapine and VSS are similar to those for alternative treatments. There is insufficient evidence on which to base conclusions on the rates of hospitalisation or the length of hospital stay associated with individual antimanic agents. Given that hospitalisation costs are the principal factor determining the total overall fixed costs associated with the management of acute mania, it is unlikely that there will be a change (increase or decrease) in NHS expenditure unless it can be shown that the period of hospital inpatient management is altered by the use of either of the newer agents.
- 6.2 The licences for the drugs considered in this guidance cover their use in the management of acute mania only, and not their potential to prevent relapse or recurrence of mania. There is currently no evidence relating to when these drugs should be discontinued after management of the acute manic episode. The Institute has therefore been unable to issue guidance on the use of these agents beyond the control of the acute symptoms associated with the manic phase of bipolar I disorder and their cost effectiveness in this context has not been evaluated.

7 Implementation and audit

- 7.1 Clinicians with responsibility for treating people with bipolar I disorder should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of people with bipolar I disorder should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

- 7.3.1 Olanzapine and VSS are considered as options for the control of the acute symptoms associated with the manic phase of bipolar I disorder.
- 7.3.2 The individual and the clinician(s) responsible for treatment decide jointly on which of the available drugs for the treatment of acute mania to use, after an informed discussion about the relative benefits and the side-effect profiles of each drug and taking into account the needs of the individual and the particular clinical situation.
- 7.3.3 When making the choice of which of the available drugs to use, in all situations where informed discussion is not possible, any advance directive is fully taken into account and the individual's advocate and/or carer is consulted when appropriate.

8 Related guidance

- 8.1 The Institute has issued guidance on the use of electroconvulsive therapy for the treatment of depressive illness, schizophrenia, catatonia and mania:
- National Institute for Clinical Excellence (2003). Guidance on the use of electroconvulsive therapy for the treatment of depressive illness, schizophrenia, catatonia and mania. *NICE Technology Appraisal Guidance* No. 59. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk
- 8.2 The Institute is also preparing guidelines on the management of bipolar disorder (anticipated publication date May 2006).

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide

whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed in July 2006.

Andrew Dillon
Chief Executive
July 2003

Appendix A. Appraisal Committee members and NICE project team.

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from contributing to any decision on guidance in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, University of Bristol

Professor Ron Akehurst

Dean, School of Health Related Research, University of Sheffield

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich

Professor Terry Feest

Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry

Ms Bethan George

Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel

Mr John Goulston

Director of Finance, St Bartholomew's Hospital & the London NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Judith Paget

Chief Executive, Caerphilly Local Health Board

Mr James Partridge

Lay Representative; Chief Executive, Changing Faces, London

Mrs Kathryn Roberts

Nurse Practitioner, Hyde, Cheshire

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Ms Anne Smith

Lay Representative; Trustee, Long Term Medical Conditions Alliance

Professor Andrew Stevens (Vice-Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner and Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Dr Sarah Garner

Technical Lead, NICE project team

Kathleen Dalby

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by NHS Centre for Reviews and Dissemination/Centre for Health Economics, University of York.

A rapid and systematic review of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder, January 2003.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- AstraZeneca¹
- Eli Lilly
- Sanofi Synthelabo

II Professional/specialist and patient/carer groups:

- British Association for Psychopharmacology
- Department of Health
- Long-Term Medical Conditions Alliance

¹ AstraZeneca was initially included as a consultee and provided a submission for its product quetiapine, which is being considered by the European Agency for the Evaluation of Medicinal Products for the treatment of acute mania. However at the time the Appraisal Committee developed its recommendations, quetiapine had not received marketing authorisation and was not considered by the Committee. AstraZeneca was therefore removed from the list of consultees and did not participate further in this appraisal.

- Manic Depression Fellowship
- Marce Society
- Mental Health Foundation
- Mind
- Mind Cymru
- National Institute for Mental Health in England
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Psychiatrists
- Royal Pharmaceutical Society of Great Britain
- SANE
- UK Advocacy Network
- UK Psychiatric Pharmacy Group
- Welsh Assembly Government
- Cambridge City Primary Care Trust
- Staffordshire Moorlands Primary Care Trust

III Commentator organisations (without the right of appeal):

- National Collaborating Centre for Mental Health
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on the use of the appraised drugs in the treatment of acute mania associated with bipolar disorder by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Margaret Edwards, Head of Strategy, SANE
- Ms P Amanda Harris, Acting Chief Executive, Manic Depression Fellowship
- Dr David Taylor, Chief Pharmacist, South London and Maudsley NHS Trust
- Professor Nigel Wellman, Professor of Health and Human Sciences, Thames Valley University, and Consultant Nurse, Berkshire Healthcare NHS Trust
- Ms Elizabeth Woodcock, Research Manager, SANE
- Professor Alan Young, Professor of General Psychiatry, University of Newcastle

Appendix C. Detail on criteria for audit of the use of olanzapine and valproate semisodium in the management of acute mania associated with bipolar I disorder

Possible objectives for an audit

An audit could be carried out to ensure that olanzapine and VSS are available for the treatment of people with acute mania associated with bipolar I disorder, and are used appropriately and effectively.

Possible patients to be included in the audit

An audit could be carried out on all people who experience the acute symptoms associated with the manic phase of associated with bipolar I disorder during a suitable time period for audit, for example, 3 to 6 months.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of olanzapine and VSS for the treatment of acute mania associated with bipolar I disorder are as follows.

Criterion	Standard	Exception	Definition of terms
1. Olanzapine and VSS are considered as options for the treatment of an individual experiencing the acute symptoms associated with the manic phase of bipolar I disorder.	100% of the people in the audit	None	Clinicians will need to agree locally on how the consideration of options is documented for audit purposes
2. The individual and the clinician(s) responsible for treatment decide jointly on which of the available drugs for the treatment of acute mania to use after an informed discussion of the following: a. the relative benefits of each drug b. the side-effect profile of each drug c. the needs of the individual d. the particular clinical situation	100% of the people in the audit	None	Clinicians will need to agree locally on how the joint decision will be documented for audit purposes
3. When making the choice of which of the available drugs to use, in all situations where informed discussion is not possible, any	100% of the people in the audit	A. The individual does not have an advance directive B. The individual does not have an advocate or carer C. It is not considered to be	Clinicians will need to agree locally on when it is not considered to be appropriate to consult an individual's advocate or carer and on how consultation with the individual's advocate or

advance directive is fully taken into account, and the individual's advocate and/or carer is consulted when appropriate.		appropriate to consult an advocate or carer	carer and consideration of an advance directive are documented, for audit purposes
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Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of the audit, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.