

82**Bipolar affective disorder**

A national clinical guideline

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May 2005

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1 ⁺⁺	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1 ⁺	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1 ⁺⁺ and directly applicable to the target population; <i>or</i> A body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺

GOOD PRACTICE POINTS

<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group
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ISBN 1 899893 29 6

First published 2005

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1 Introduction

1.1 BACKGROUND

Bipolar affective disorder is relatively common, with a lifetime prevalence of approximately 1.3%.^{1,2} It occurs in all age groups and in its most severe form is equally distributed between the sexes.¹ The illness can interfere repeatedly and sometimes profoundly with patients' well-being and productivity and can be associated with increased morbidity and mortality. The unpredictable natural history of bipolar affective disorder makes research into therapeutic options difficult.³

1.2 THE NEED FOR A GUIDELINE

Bipolar affective disorder is difficult to diagnose, particularly if individuals are only seen during the depressive phase.⁴ Bipolar affective disorders are often associated with creativity, but sufferers may have additional psychological and social problems associated with their condition.³ Drugs are available for the treatment of individuals with bipolar affective disorders but their use requires careful management with regular follow up. As in other long term medical conditions, approximately 50% of individuals do not take their prescribed medication.⁵ Psychosocial interventions have also been introduced and evaluated, but need to be brought to more general attention. Previous guidelines have concentrated on expert reviews of literature and clinical practice. This guideline is based on critical appraisal of the primary evidence.⁶⁻⁸

1.2.1 MORBIDITY AND MORTALITY

Comorbid illness occurs more often with bipolar affective disorder than would be expected by chance and is often attributable to lifestyle factors as a direct result of the bipolar affective disorder. The condition is associated with a mortality rate, due to any cause, that is two to three times greater than that of the general population.³ Between 10 and 20% of individuals with bipolar disorder take their own life, mainly in a depressive or mixed episode, and nearly one third of patients admit to at least one suicide attempt.³

1.2.2 NATURAL HISTORY

The peak age of onset of bipolar affective disorder is in the mid-teen to mid-twenties range, although treatment is often not obtained until up to a decade after onset. More than 10% of adolescents presenting with recurrent depression will develop bipolar affective disorder. Adolescents may also present with long standing behaviour problems before a clear cut manic or hypomanic episode occurs.¹

The course of the illness is highly unpredictable; while 90% of patients have a recurrence once they have suffered a manic episode,³ only 10 to 15% of patients present as "rapid cyclers" with more than three episodes per year with partial or full remissions in between, or switch to the opposite polarity (manic to depressed or vice versa).¹ Some patients have persistent disability with low-grade symptoms and cognitive deficits between acute episodes.⁹

First presentation with mania at over 60 years of age is likely to be associated with underlying organic illness. Earlier onset is more closely linked with genetic factors, although the details of inheritance and the genes involved remain unknown.^{1,10}

1.3 LIMITS OF THE AVAILABLE EVIDENCE

Bipolar affective disorder is one of the less well researched serious and enduring mental illnesses.¹¹ One of the reasons for this is that bipolar affective disorder is a reversible episodic condition. Spontaneous remissions occur regularly, even within the usual interval of six weeks used for acute treatment studies. The selection of patients may have a crucial effect on recovery rates. Uncontrolled studies will not provide clear evidence for or against the efficacy of any given treatment.

Both depressive and manic episodes of bipolar affective disorder affect the researcher's ability to recruit patients into randomised controlled trials (RCTs). The necessary selection of patients with milder manifestations of the illness, particularly for placebo-controlled designs, may also prejudice the ability to generalise to more severe episodes of the illness.⁷

Long term prevention of illness relapse is an important treatment aim. Although an acutely effective treatment is likely to prevent similar symptoms later on, the bipolar nature of the illness makes it possible that an acutely effective treatment may cause a reversal (switch) of symptoms, ie from depression to mania. The goal of finding genuine mood stabilisers has not yet been realised.^{6,12}

The difficulties of incorporating new evidence into established practice has also been acknowledged. Older treatment trials are often less methodologically sound, but have the support of long term clinical experience, evidence extrapolation and opportunity for meta-analysis. New treatments are typically presented with robust trial evidence but may lack comparison with agents other than placebo. Caution in comparing the strength of evidence across time is advisable.

Studies which assess the effect of severe parental mental illness on children were not considered in the guideline. The results from studies of patients with mental illness in general have not been extrapolated to patients with bipolar affective disorder. Specifically, non-pharmacological interventions relating to major mental illness in general, were discarded because their applicability to bipolar affective disorder is not clear.

1.4 THE LEGAL FRAMEWORK IN SCOTLAND

The legal framework underpinning treatment relies on the informed consent of the patient. The law provides for the small minority of cases when an element of compulsion is necessary. The Mental Health (Scotland) Act 1984 has been replaced by the Mental Health (Care and Treatment) (Scotland) Act 2003. The Adults with Incapacity Act 2000, was implemented in 2002. These acts describe the circumstances and provide safeguards for treatment and care where a person's capacity to consent or to make decisions is impaired. Codes of practice supporting the use of legislation and giving more detailed guidance will have a major impact on practice, staffing and resources in the mental health sector.

1.5 REMIT OF THE GUIDELINE

This guideline covers adults (aged 18 years or over) with bipolar affective disorders. A discussion of diagnostic issues in adolescence is included because of the often early onset of the condition.

1.6 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is, however, advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.7 REVIEW AND UPDATING

This guideline was issued in 2005 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

2 Definitions and diagnosis

2.1 DEFINITIONS

There are two main diagnostic schemes defining bipolar affective disorder; the International Classification of Diseases of the World Health Organisation (10th edition ICD-10) and the Diagnostic and Statistical Manual (4th edition DSM-IV) of the American Psychiatric Association.^{1,13,14} The schemes use mostly equivalent diagnostic categories, with the DSM-IV dividing bipolar disorder into bipolar I and bipolar II (see *Table 1*).

Bipolar affective disorder is characterised by repeated episodes in which the patient's mood and activity levels are significantly disturbed, with on some occasions, an elevation of mood and increased energy and activity (mania or hypomania, see *section 2.1.1*), and on others a lowering of mood and decreased energy and activity (depression, see *section 2.1.2*). Patients who suffer only from repeated episodes of mania are comparatively rare, and are classified as having bipolar affective disorder. Such patients resemble (in their family history, pre-morbid personality, age of onset, and long term prognosis) those who also have at least occasional episodes of depression.

Manic episodes usually begin abruptly and last for between two weeks and four to five months (median duration about four months). Depressions tend to last longer (median length about six months), though rarely for more than a year, except in the elderly. Episodes of both kinds often follow stressful life events or other mental trauma, but the presence of such stress is not essential for the diagnosis. The first episode may occur at any age from childhood to old age. The frequency of episodes and the pattern of remissions and relapses are both very variable, though remissions tend to get shorter as time goes on and depressions become commoner and longer lasting after middle age.¹

While the WHO's ICD-10 diagnostic system is generally applied in Scottish clinical practice, many research studies have been published using DSM clinical or other research criteria. Because DSM-IV and ICD-10 define certain disorders in a subtly different fashion, reference has been made to the relevant diagnostic system used when discussing results. For example, ICD-10 and DSM-IV "hypomania" are not identical (see *Table 1*).

The reported prevalence of bipolar affective disorder in a community depends on the diagnostic scheme used and subcategory. Estimates of lifetime prevalence of bipolar disorder (DSM-IV bipolar I) range from 0.4 to 1.6%.¹ The epidemiology of bipolar II disorder is less well established, but its prevalence may be as high as 1.5 – 2.5%.¹⁵

Table 1: Comparison of ICD-10/DCR-10^{13, 14} and DSM-IV

ICD-10/DCR-10	DSM-IV
<p>F30.0 Hypomania</p> <p>For at least four days persistent mild elevation or irritability of mood and presence of at least three of the following: increased energy and activity, increased sociability, talkativeness, over-familiarity, mild overspending or other types of reckless and irresponsible behaviour, increased sexual energy, decreased need for sleep and difficulty in concentration or distractibility.</p> <p>Symptoms do not lead to severe disruption of work or result in social rejection. The disturbances of mood and behaviour are not accompanied by hallucinations or delusions.</p>	<p>296.40 Hypomanic episode</p> <p>For at least four days sustained elevated, expansive or irritable mood different from the patient's usual non-depressed mood and persistence of at least three symptoms (at least four if the only abnormality of mood is irritability). Grandiosity or exaggerated self-esteem, reduced need for sleep, increased talkativeness, flight of ideas or racing thoughts, easy distractibility, psychomotor agitation or increased goal-directed activity (social, sexual, work or school), poor judgment (as shown by spending sprees, sexual adventures, foolish investments).</p> <p>There are no features of psychosis (delusions, hallucinations, bizarre behaviour or speech). The episode does not require hospitalisation or markedly impair work, social or personal functioning.</p>
<p>F30.1 Mania without psychotic symptoms</p> <p>For at least one week (or less, if hospitalised): Mood elevated, expansive or irritable out of keeping with the patient's circumstances. At least three of the following have to be present: increased activity or physical restlessness, pressure of speech, flight of ideas or racing thoughts, loss of normal social inhibitions, decreased need for sleep, distractibility or constant changes in plans, inflated self esteem with grandiose ideas and overconfidence, behaviour that is foolhardy and reckless, marked sexual energy or indiscretion.</p> <p>F30.2 Mania with psychotic symptoms</p> <p>In addition to F30.1, delusions (usually grandiose) or hallucinations (usually of voices speaking directly to the patient) are present, or the excitement, excessive motor activity, and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication.</p>	<p>296.4x Manic episode</p> <p>For at least one week (or less, if hospitalised) the patient's mood is abnormally and persistently high, irritable or expansive. To a material degree during this time, the patient has persistently had three or more of these symptoms (four or more if the only abnormality of mood is irritability): grandiosity or exaggerated self esteem, reduced need for sleep, increased talkativeness, flight of ideas or racing thoughts, easy distractibility, psychomotor agitation or increased goal-directed activity (social, sexual, work or school), poor judgment (as shown by spending sprees, sexual adventures, foolish investments).</p> <p>Symptom severity results in (at least one) material distress, psychotic features, hospitalisation to protect the patient or others, impaired work, social or personal functioning.</p> <p>Further subgroups:</p> <ol style="list-style-type: none"> (1) Mild. Symptoms barely meet criteria for an episode of mania. (2) Moderate. There is an extreme increase in either activity level or impaired judgment. (3) Severe without psychotic features. The patient requires nearly continuous supervision to prevent physical harm to self or to others. (4) Severe with psychotic features. The patient has delusions or hallucinations, which may be mood-congruent or mood-incongruent.

Table 1 continued

<p>F31 Bipolar affective disorder</p> <p>Multiple episodes of mania/hypomania or both depression and mania/hypomania; current episodes as defined above or below:</p>	<p>296.xx Bipolar I disorder</p> <p>One or more manic episodes or mixed episodes. Individuals often have one or more major depressive episodes.</p> <p>296.89 Bipolar II disorder</p> <p>One or more major depressive episodes accompanied by at least one hypomanic episode.</p>
<p>F31.6 Bipolar affective disorder, current episode mixed</p> <p>The patient has had at least one authenticated hypomanic, manic, depressive, or mixed affective episode in the past, and currently exhibits either a mixture or a rapid alteration of manic and depressive symptoms.</p>	<p>296.6x Mixed episode</p> <p>Fulfilled symptom criteria for both major depressive and manic episodes nearly every day for a week or more. The symptoms are severe enough that they (at least one) include psychotic features, require hospitalisation to protect the patient or others, impair work, social or personal functioning.</p>
<p>F32 Depressive episode</p> <p>Patient suffers from two weeks of lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self esteem and self confidence are almost always reduced and, even in the mild form, ideas of guilt or worthlessness are often present. Low mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasure, waking in the morning hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido.</p> <p>Depressive episodes may be specified as mild (at least four symptoms), moderate (at least six and difficulty continuing with ordinary activities) or severe (at least eight, symptoms are marked and distressing).</p>	<p>296.5x Major depressive episode</p> <p>Two weeks of > four symptoms/signs including depressed mood or decreased interest or pleasure (obligatory), and marked loss or gain of weight or appetite; excessive or not enough sleep; patient's activity is agitated or retarded; fatigue or loss of energy; patient feels worthless or inappropriately guilty; is indecisive or has trouble thinking or concentrating; repeated thoughts about death (other than the fear of dying), suicide (with or without a plan) or suicide attempt.</p> <p>These symptoms cause clinically important distress or impair work, social or personal functioning.</p> <p>Episode did not start within two months of the loss of a loved one (unless the symptoms are severe, defined as severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions or hallucinations or psychomotor retardation).</p>

2.1.1 SIGNS AND SYMPTOMS OF MANIA AND HYPOMANIA

Signs and symptoms of mania (or a manic episode) include (see *also Table 1*):¹⁶

- increased energy, activity, and restlessness
- excessively high, overly good, euphoric mood
- extreme irritability
- racing thoughts and talking very fast, jumping from one idea to another
- distractibility, cannot concentrate well
- little sleep needed
- unrealistic beliefs in one's abilities and powers
- poor judgement
- spending sprees
- a lasting period of behaviour that is different from usual
- increased sexual drive
- abuse of drugs, particularly cocaine, alcohol, and sleeping medications
- provocative, intrusive, or aggressive behaviour
- denial that anything is wrong

2.1.2 SIGNS AND SYMPTOMS OF DEPRESSION

Signs and symptoms of depression (or a depressive episode) include:¹⁶

- lasting sad, anxious, or empty mood
- feelings of hopelessness or pessimism
- feelings of guilt, worthlessness, or helplessness
- loss of interest or pleasure in activities once enjoyed, including sex
- decreased energy, a feeling of fatigue or of being slowed down
- difficulty concentrating, remembering, making decisions
- restlessness or irritability
- sleeping too much, or can't sleep
- change in appetite and/or unintended weight loss or gain
- chronic pain or other persistent bodily symptoms not caused by physical illness or injury
- thoughts of death or suicide, or suicide attempts

2.1.3 PSYCHOTIC SYMPTOMS

Severe episodes of mania or depression can include psychotic symptoms. Common psychotic symptoms are:

- hallucinations (hearing, seeing, or otherwise sensing the presence of things that are not actually there and cannot be sensed by others)
- delusions (false, strongly held beliefs not influenced by logical reasoning or explained by a person's usual cultural concepts)
- inability to communicate due to markedly speeded up, slowed down or distorted speech (thought disorder, flight of ideas, psychomotor slowing).

Psychotic symptoms in bipolar disorder often reflect the extreme mood state at the time (are mood congruous). For example, delusions of grandeur, such as believing one is royalty or has special powers or wealth, may occur during mania; delusions of guilt or worthlessness, such as believing that one is ruined and penniless or has committed some terrible crime, may appear during depression. Mood incongruous psychotic experiences, ie that do not fit into the general mood of the patient, can also occur. People with bipolar disorder who have these symptoms are sometimes incorrectly diagnosed as having schizophrenia.¹⁶

2.1.4 MIXED AFFECTIVE STATES

Symptoms of mania and depression can occur together in a condition called a mixed (affective) state (ICD-10: F31.6, DSM-IV: 296.6x; see *Table 1*). Symptoms include agitation, trouble sleeping, significant change in appetite, psychotic symptoms and suicidal thinking. A person may have a very sad, hopeless mood while at the same time feeling extremely energised.¹⁶

2.2 DIAGNOSIS

The diagnosis of bipolar illness relies upon clinical assessment. Diagnosis is based upon criteria listed in ICD-10 or DSM-IV (see *section 2.1*). The Scheduled Clinical Interview for DSM (SCID) is the standard research tool to identify psychiatric disorder in DSM-IV classification.¹⁷ Other research interview schedules such as the Present State Examination (PSE) can be used for ICD-10 diagnostic coding. These instruments are mainly research tools but can be used as adjuncts to the gold standard of clinical diagnosis.

2.2.1 DELAY IN DIAGNOSIS

Delays to an accurate diagnosis can extend to many years and may be associated with instability of presentation.¹⁸ In an adult cohort of patients experiencing a first psychotic episode, only 75% kept their diagnosis of bipolar illness after six months.¹⁸ Confusion with schizophrenia, schizoaffective disorder or psychotic depression may occur. Delay may also be due to the late occurrence of manic or hypomanic episodes in the context of recurrent depressive illness, or late presentation of illness.

2+

- Early and accurate diagnosis should be attempted to allow treatment as soon as possible after a first episode.

2.2.2 EARLY DETECTION

Little evidence was identified regarding the early or prodromal symptoms of bipolar illness that allow predictions of illness to be made. Early symptoms have been mainly examined in non-representative communities making it difficult to extrapolate these results to patients with bipolar affective disorder.¹⁹

2+

There is insufficient evidence to make a recommendation on the use of screening tools for the early identification of bipolar affective disorder. No specific evidence was identified on the impact of pre-symptomatic treatment on outcome.

2.2.3 DIAGNOSTIC SCALES

Bipolar disorder can be assessed using rating scales which can be divided into diagnostic scales and measures of severity. Only diagnostic scales are considered in the guideline. Diagnostic scales are compared against the gold standard of clinical assessment.

Table 2: Diagnostic scales for bipolar affective disorder

Scale	Sensitivity	Specificity
Clinician-Administered Rating Scale for Mania (CARS-M) ²⁰	0.85	0.87
Mini International Neuropsychiatric Inventory (MINI) ²¹	0.89	0.97
Psychosis Screening Questionnaire (PSQ) ²²	0.96	0.95
Mood Disorder Questionnaire (MDQ) ²³	0.72	0.90
Brief Psychiatric Rating Scale (BPRS) ²⁴	0.67	0.72

The absence of a gold standard distinct from clinical diagnosis makes it impossible to compare the accuracy of the above scales with clinical assessment. Of the five scales listed above, the three best validated for first admission bipolar patients are the PSQ, MDQ, and BPRS.²²⁻²⁴ There is no evidence that demonstrates superiority of rating scales over clinical assessment. 2+

D A diagnosis of bipolar affective disorder should be made after clinical assessment according to DSM or ICD criteria.

Clinicians should be aware of the instability of diagnosis during clinical review of patients with affective disorder.

2.2.4 DIAGNOSTIC SCALES IN DIFFERENT PATIENT GROUPS

Insufficient evidence was identified to comment on the use of diagnostic screening tools in specific patient groups, eg people seeking treatment for substance misuse, people with a learning disability or the elderly.

2.3 GENETIC RISK

The lifetime prevalence of bipolar I disorder in community samples ranges from 0.5 to 1.5%. This rises to 4-9% in their first degree biological relatives.²⁵ There is also a raised rate of bipolar II disorder (1-5%)¹ and major depressive disorder (8-20%)²⁵ in these relatives. A combination of twin and adoption studies suggests that a substantial proportion of illness risk is genetic.²⁵ Due to the absence of a reliable genetic or an early fetal marker, genetic counselling is limited to providing information on these wide ranges of risk.

3 Acute treatment

Most treatment studies concentrate on bipolar I disorder. As little evidence exists for the specific treatment of patients with bipolar II, recommendations have been extrapolated from evidence relating to patients with bipolar I or a mixture of patients with bipolar I or bipolar II. Patients in acute treatment trials may be more likely to suffer from hypomania or mild mania which should be borne in mind when interpreting results. Little evidence exists for adolescent and elderly patients with bipolar affective disorder or for patients with bipolar affective disorder and additional illnesses or disabilities. Little is known about the optimal duration of antimanic treatments. This leads to a lack of evidence about continuing treatment and relapse prevention (see section 4). A general, but formally untested clinical assumption is that effective antimanic treatments may also be effective prophylactics and long term treatments. Advance directives or similar arrangements can be usefully employed to anticipate the need for active intervention and treatment of a manic episode while the patients are well.

The prescription of any medication requires an assessment of risk and of benefit. In this guideline the efficacy and safety of medications for bipolar disorders have been reviewed using the best available evidence. Where recommendations are graded for individual drugs, this is done irrespective of the licensing status of that product. This applies to clonazepam and lamotrigine, which are currently unlicensed for the indications described, and olanzapine, for the treatment of bipolar depression. Further details are included in sections 3 and 4 where appropriate.

3.1 MANIA

3.1.1 ANTIPSYCHOTIC DRUGS

Antipsychotic drugs have been used for the treatment of mania in Europe and the USA for the past fifty years. The published trial evidence for newer drugs, such as olanzapine, quetiapine and risperidone, is balanced by decades of clinical experience with older antipsychotic drugs, such as chlorpromazine, haloperidol and perphenazine. They may also be prescribed for associated indications, such as psychomotor agitation, excitement and violent or dangerously impulsive behaviour in the setting of acute mania.

Chlorpromazine, haloperidol and perphenazine

There is little placebo-controlled trial information to show that older (typical) antipsychotic drugs specifically treat the symptoms of acute mania.²⁶ Because of their long established use, some of these drugs have been used as the “gold standard” to validate effectiveness of some of the newer drugs.²⁷⁻³⁰

Olanzapine

Olanzapine may be more effective in acute mania than placebo and semisodium valproate and equivalent to haloperidol.³¹ Weight gain and extrapyramidal symptoms are a greater problem with olanzapine than with semisodium valproate. Olanzapine caused greater weight gain, but less extrapyramidal side effects than haloperidol. The studies included in this review are potentially biased by high drop-out rates.³¹ Intramuscular olanzapine may be more effective in reduction of manic agitation and overactivity than placebo.³²

1+

Quetiapine and risperidone

Quetiapine and risperidone have been licensed in the UK for the treatment of mania.³³ No specific recommendations about their use in mania have been made given the insufficient body of evidence available at the time of publication. Quetiapine in combination with either lithium or valproate in acute mania is more efficacious than either lithium or valproate monotherapy.³⁴

1+

3.1.2 VALPROIC ACID SALTS

The effectiveness of semisodium valproate in mania over placebo has been demonstrated in a good quality systematic review (n = 316).³⁵ There was no difference in efficacy between semisodium valproate and lithium (n = 158) or carbamazepine (n = 59), although semisodium valproate was less effective than olanzapine (n = 363; see *section 3.1.1*).³⁵ 1+
1-

Two valproic acid salts are currently (May 2005) licensed in the UK – semisodium valproate for acute mania and sodium valproate for epilepsy. Nearly all of the reviewed evidence on valproic acid relates to studies of semisodium valproate in the treatment of acute mania.

There are no ‘head to head’ comparisons of sodium valproate and semisodium valproate in the treatment of mania, so superiority of one over the other has not been established. Semisodium valproate and sodium valproate preparations are not equipotent, resulting in different dosage requirements. Although the therapeutic component appears to be the valproate ion, there are differences in pharmacokinetics and tolerability between different preparations in that semisodium valproate possibly achieves higher plasma levels more rapidly and appears to cause fewer gastrointestinal side effects.^{36,37}

3.1.3 CARBAMAZEPINE

No placebo controlled RCTs were identified. Two RCTs found an equivalent response between carbamazepine and lithium (n = 155).^{38,39} Two RCTs found equivalence with haloperidol (n = 53).^{27,40} There is insufficient evidence to make a recommendation. 1+

3.1.4 OTHER ANTICONVULSANTS

Two small trials were identified relating to the use of lamotrigine and phenytoin in acute mania.^{41,42} There is insufficient evidence to make a recommendation. 1-

3.1.5 LITHIUM

Lithium has been used as the “gold standard” in RCTs of some of the newer antimanic treatments.^{38,41,43,44} There is evidence to support the use of lithium in combination with an antipsychotic in patients who have developed manic symptoms whilst receiving lithium maintenance treatment.^{29,30,45} 1+

3.1.6 BENZODIAZEPINES

Three RCTs support the efficacy of lorazepam and clonazepam in acute mania, especially in acutely agitated patients where sedation is a priority.⁴⁶⁻⁴⁸ 1+

3.1.7 ELECTROCONVULSIVE TREATMENT (ECT)

The successful use of ECT has been described in treatment resistant severe mania. The National Institute of Clinical Excellence (NICE) guidance for the use of ECT recommends its use in this context as weakly supported by evidence.⁴⁹ 3

3.1.8 RECOMMENDATIONS FOR THE TREATMENT OF ACUTE MANIA

- A**
- Acute manic episodes should be treated with oral administration of an antipsychotic drug or semisodium valproate.
 - Lithium can be used if immediate control of overactive or dangerous behaviour is not needed or otherwise should be used in combination with an antipsychotic.
- ☑ Intramuscular injection of antipsychotics and/or benzodiazepines (lorazepam), should be used in emergency situations, in accordance with local protocols.
 - ☑ Benzodiazepines may be used as adjunctive treatment in acute mania where sedation is a priority.
 - ☑ Patients who suffer an acute manic episode whilst on maintenance treatment with an antimanic drug should have their dose of antimanic drug optimised. Treatment with an antipsychotic or valproic acid should be initiated as appropriate.
 - ☑ Severe, treatment-resistant mania may require electroconvulsive treatment to avert harm due to the illness.
 - ☑ Combination therapy with several antimanic agents from different classes may be required in treatment resistant cases.
 - ☑ Duration of treatment will be determined by the reduction of symptoms, the emergence of side effects and the need to provide treatment for residual symptoms and prevent relapse (see section 4).
 - ☑ Antidepressant drug treatment should be reduced and discontinued during an acute manic episode (see section 3.2.1).
 - ☑ A clear terminology should be implemented to avoid confusion in the prescription of sodium valproate and semisodium valproate, as well as the different lithium salts and preparations.

3.2 DEPRESSION

The vast majority of people treated for depression suffer from unipolar depression and this is reflected in the evidence available.⁵⁰ Most treatment trials target unipolar patients but will, by default, include some patients who later develop a manic illness. The evidence from unipolar trials may not be directly transferrable to patients with bipolar disorder, but may have some limited relevance. The potential risks of treating bipolar depression are the triggering of a manic or hypomanic episode and the precipitation of rapid cycling. While there is good evidence for the former, the latter is controversial.⁵¹

No evidence to support the use of antidepressant drugs in the treatment of mixed affective states was identified.

3.2.1 ANTIDEPRESSANT DRUGS

Large numbers of randomised placebo-controlled studies of antidepressant drugs have been carried out in patients with mainly unipolar depression. The effect of these drugs on patients with bipolar depression can only be extrapolated.⁵² Tricyclic antidepressants are more likely to trigger manic episodes than some newer antidepressants and patients with bipolar II are less likely to switch to mania when given antidepressants.^{15,53-55} Little evidence exists about the ideal length of antidepressant use in patients with bipolar. Because of the risk of triggering manic episodes or possibly rapid cycling, prescribing will be more conservative than, for example, in unipolar depression. Optimal duration of treatment may have to be determined by experience in every patient. A meta-analysis supports the short-term use of antidepressants in patients with bipolar depression, with little evidence of early switching to mania with antidepressants other than tricyclics.⁵⁶

1+

4

1+

- 3.2.2 LITHIUM
Despite widespread use in clinical practice there is limited evidence to support the efficacy of lithium alone in patients with bipolar depression.^{57,58} 4
- 3.2.3 LAMOTRIGINE
There is accumulating evidence for the effectiveness of lamotrigine alone or in combination with antidepressants as an effective drug for this indication, although the number of patients treated is still small.^{59,60} 1+
- 3.2.4 ELECTROCONVULSIVE THERAPY
There are no controlled trials of ECT specifically related to bipolar depression. A systematic review of RCTs and observational studies supports the use of ECT in severe and psychotic depression.⁶¹ 1+
- 3.2.5 ANTIPSYCHOTIC DRUGS
There is no published evidence to support the use of antipsychotics as monotherapy in bipolar depression. There is one study suggesting that olanzapine, particularly in combination with fluoxetine, was more effective than placebo in the treatment of this condition.⁶² 1+
- 3.2.6 RECOMMENDATIONS FOR THE TREATMENT OF ACUTE DEPRESSION

B An antidepressant in combination with an antimanic drug (*lithium, semisodium valproate or an antipsychotic drug*), or lamotrigine is recommended for the treatment of acute bipolar depression in patients with a history of mania.

- Patients maintained on mood stabilisers who suffer a depressive episode should be started on an antidepressant after optimising their mood stabiliser.
- Interactions between serotonergic antidepressants, antipsychotic drugs and lithium and the risk of triggering mania or rapid cycling should be considered when selecting an antidepressant.
- ECT should be considered for patients with bipolar depression who are at high risk of suicide or self harm.

3.3 RAPID CYCLING AND MIXED AFFECTIVE STATES

Rapid cycling bipolar disorder is defined by the occurrence of four or more illness episodes per year. It occurs in up to 20% of patients with bipolar affective disorder.⁶³⁻⁶⁷ Although some studies have shown that lithium is less effective in rapid cycling,^{68,69} this has not always been replicated.^{67,70,71} Antipsychotic drugs have been found to be useful.^{72,73} Anticonvulsant mood stabilisers may also be effective in treating mania and preventing relapse from rapid cycling disorder.^{74,75}

Mixed affective states are characterised by combinations of manic and depressive symptoms during one episode and may occur in up to 40% of bipolar patients.^{76,77} Sixty six percent of these patients exhibit a poor response to lithium, and valproate may be more effective.^{35,78} Mixed affective states have been insufficiently researched to arrive at definitive recommendations for treatment.

4 Maintenance

The treatment of one phase of bipolar affective disorder may trigger the opposite phase, such that antidepressants may trigger manic episodes or even rapid cycling. The prevention of relapse may often require complex treatment strategies.^{12,51,79}

4.1 PHARMACOLOGICAL RELAPSE PREVENTION

Drug licensing in the UK is discussed in section 3. The drug therapy studies reviewed in this section do not take licensing status into consideration. Lamotrigine is currently unlicensed for prophylaxis and carbamazepine is licensed in the UK only for patients who are unresponsive to lithium.

4.1.1 LITHIUM

Three small but well conducted meta-analyses indicate that lithium prophylaxis is effective in reducing early and later relapse in patients with bipolar affective disorder for up to three years.⁸⁰⁻⁸² The prophylactic effect of lithium is greatest for the prevention of manic and hypomanic episodes (relative risk: 0.62, 95% confidence interval: 0.40–0.95) and marginal with respect to depressive episodes (RR: 0.72, 95% CI: 0.49–1.07).⁸² Higher lithium blood levels (>0.7 mmol/l) are more effective than lower levels, and daily dosing is more effective than dosing every second day.^{83,84} Sudden withdrawal of lithium may lead to a provocation of manic symptoms.^{81,85-87}

1+
4

- A** Lithium is the treatment of choice for relapse prevention in bipolar affective illness.
- A** Lithium should be prescribed at an appropriate dose with a daily dosing regimen.
- A** The withdrawal of lithium should be gradual to minimise the risk of relapse.

Lithium has a narrow therapeutic margin, and side effects are relatively common and potentially severe. Side effects include polyuria and polydipsia, hypothyroidism, gastrointestinal disturbance and tremor. Toxicity occurs at 150% of the upper limit of the therapeutic dose range and may develop as a result of reduced kidney function during general physical illness, or through adverse interactions with other medications, such as diuretics and non-steroidal anti-inflammatory drugs.

2+

Patients may experience reversible changes in their ability to process information during lithium treatment, and this may have relevance to their driving skills.⁸⁸

2+

Long term treatment with lithium may show faster age related reduction in kidney function, although very few incidences of kidney failure requiring dialysis have been reported.⁸⁹⁻⁹¹

3
4

- In general practice, lithium should be prescribed in the context of a shared care protocol to minimise side effects and toxicity.
- Before embarking on maintenance treatment with lithium, patient and doctor should consider severity of the last episode, number, frequency and severity of previous episodes, personal factors, such as a wish to become pregnant or the wish to avoid sick leave from work or education. Patient concordance and ability to take regular medication will be essential for some treatments (lithium), but not for others (depot antipsychotic medication).

4.1.2 CARBAMAZEPINE

Carbamazepine may be as effective as lithium in preventing relapse over six weeks to three years,^{38,39,92-97} although two studies (n = 144 and n = 94) report superiority of lithium over carbamazepine in patients with bipolar I,^{98,99} and one of these suggests equivalent efficacy for both drugs in patients with bipolar II disorder.⁹⁸

1+

A Carbamazepine can be used as an alternative to lithium, particularly in patients with bipolar II, or when lithium is ineffective or unacceptable.

The effect of long term carbamazepine prescription on the metabolism of other prescription drugs should be considered.

4.1.3 VALPROIC ACID SALTS

One trial examined the use of semisodium valproate in the maintenance treatment of patients with bipolar illness over one year, compared with lithium or placebo (n = 187).¹⁰⁰ Although this study showed no difference between semisodium valproate and lithium, there was also no superiority of either treatment over placebo, possibly because of the low severity of illness in the selected treatment group. Although many patients, who respond to semisodium valproate during an acute manic episode, may continue by default on this medication after remission of the episode, there is insufficient evidence to recommend valproic acid salts as an alternative to lithium in the maintenance treatment of bipolar affective disorder.

1-

4.1.4 LAMOTRIGINE

An RCT of 638 patients with bipolar I with recent hypomanic or manic or depressive episodes found that after stabilisation, continuation with lamotrigine over 18 months delayed the onset of the next depressive episode, while continued prophylaxis with lithium delayed the onset of the next manic or mixed affective episode.^{101,102} A further small crossover RCT (n = 37) demonstrates the superior efficacy of lamotrigine over placebo and gabapentine.¹⁰³

1+

A Lamotrigine can be used for prophylaxis in patients who have initially stabilised with lamotrigine, particularly if depressive relapse is a greater problem than manic relapse.

4.1.5 ANTIPSYCHOTIC MEDICATIONS

As antipsychotic drugs have proven efficacy in the treatment of acute manic episodes (see section 3.1.1), they are sometimes continued beyond the acute episode and assumed to have prophylactic value. Potential problems are the absence of antidepressant effects and the risk of tardive movement disorders. Clinical advantages include the availability of depot preparations, the absence of well known rebound phenomena, such as can be observed with lithium and relative safety (particularly of the older drugs) in pregnancy. Antipsychotic drugs may be a more practical alternative over the recommended options (see sections 4.1.1, 4.1.2, 4.1.4) in the longer term management of certain patients with bipolar disorder, such as patients who do not comply with oral medication and as a consequence suffer frequent relapse, or patients liable to become pregnant or who are pregnant (see section 5.4.5).

4.1.6 ANTIDEPRESSANT DRUGS

While antidepressant drugs are effective in the short term treatment of patients with bipolar depression (see section 3.2.1), they have the potential to induce switching to hypomania or mania and long term monotherapy with (especially tricyclic) antidepressants is not advisable.

4.2 CONCORDANCE

The efficacy of most medical interventions depends on the cooperation of the patient. The term “concordance” has been used synonymously with the older terms “adherence” and “compliance”.

There is only limited evidence on concordance in patients with bipolar affective disorder. Three papers were identified, with two looking at concordance in euthymic bipolar patients on long term mood stabilisers.¹⁰⁴⁻¹⁰⁶ Severity of illness, demography or number and type of medication did not seem to be associated with non-concordance. Non-concordance was associated with comorbidity, substance abuse and negative attitudes to medication, treatment and prophylaxis. There was some evidence that concordance was reduced with increasing length of treatment.¹⁰⁶ No recommendations can be made regarding methods to improve concordance, specifically in bipolar disorder. Packages of psychosocial interventions that include “concordance therapy” are discussed in section 4.3.

2-

4.3 PSYCHOSOCIAL INTERVENTIONS

There is a large literature describing the psychotherapy of depression. This literature is explicitly or implicitly limited to patients with a unipolar course of illness, or at best includes some patients with bipolar disorder depression. Recommendations for the treatment of bipolar depression can only be made by extrapolating from evidence collected from depressed patients. For this reason, the section on psychosocial interventions is limited to maintenance of recovery in patients with bipolar affective disorder.

Psychosocial interventions include a variety of approaches such as befriending, cognitive behavioural therapy, dialectical behavioural therapy, family therapy, interpersonal therapy, patient education, psychoanalytical psychotherapy, self help groups, self management, support networks and other psychological and/or psychosocial packages.

4.3.1 COGNITIVE BEHAVIOURAL THERAPY (CBT)

Cognitive behavioural therapy is a treatment based on the assumption that thinking, mood and behaviour affect one another. Therapists aim to teach patients techniques to monitor, examine and change the dysfunctional thinking and behaviour associated with undesirable mood states.¹⁰⁷

Three good quality UK trials of CBT versus either treatment as usual or a waiting list control, show a benefit from seven to 25 sessions of CBT for both relapse prevention and improved social functioning over follow up periods of up to 18 months.¹⁰⁷⁻¹⁰⁹

The CBT interventions in these studies were adapted to use in patients with bipolar affective disorders by incorporating early warning signs monitoring. This involves training patients to identify possible prodromal features of manic or depressive relapse, ie the relapse ‘signature’. Early warning signs monitoring also involves developing a list of ‘at risk’ situations and producing and rehearsing an action plan once prodromes have been recognised by the patient.¹⁰⁹

1+

Two of these studies also examined cognitive and behavioural approaches to enhance self management of depressive and hypomanic symptoms and to establish regular activity patterns such as daily routines and regular sleep patterns.^{108,109}

Preliminary indications from a small open study are that concordance therapy, an abbreviated model of cognitive therapy, may be effective in improving adherence with lithium prophylaxis.¹¹⁰

3

Another small open study of patients initially responsive to lithium who were treated with CBT after a relapse found that time to relapse after CBT was longer than time to relapse before CBT.¹¹¹

3

4.3.2 INTERPERSONAL AND SOCIAL RHYTHM THERAPY (IPSRT)

IPSRT focuses on the impact of disrupted social rhythms, teaching patients with bipolar disorder to regularise their sleep-wake patterns, work, exercise, meal times and other daily activities,¹¹²⁻¹¹⁴ in addition to the focus on interpersonal problem areas characteristic of interpersonal therapy.¹¹²

1+

4.3.3 BEHAVIOURAL FAMILY THERAPY

Behavioural family therapies for bipolar affective disorder have three main components: psychoeducation, communication enhancement training and problem-solving skills training including development of a 'relapse drill'. The intervention is designed to improve family functioning, improve mood and reduce risk of relapse.

An adaptation of behavioural family therapy, with a focus on couples or families of patients with bipolar affective disorder has been shown to be beneficial.^{115,116} Members of families who received nine months of family focused therapy (FFT) showed significant improvement in family functioning.¹¹⁵ Follow up over two years demonstrated fewer relapses and longer survival intervals for patients who received FFT compared with those who received the crisis management intervention.¹¹⁷ FFT has a significant benefit compared with individually focused patient treatment in reducing rates of hospitalisation for affective episodes (55% versus 88%).¹¹⁸

1+

4.3.4 GROUP PSYCHOEDUCATION

A group psychoeducational approach, over 21 sessions, had a greater success in relapse prevention compared with attendance for the same number of sessions at unstructured group meetings.¹¹⁹ Group psychoeducation was focused on improving four main issues: illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and life style regularity.

1+

4.3.5 AREAS OF OVERLAP IN TREATMENTS

There are areas of overlap between the available psychosocial interventions. There are similarities between the social rhythm monitoring of IPSRT and the monitoring of early warning signs in CBT. Psychoeducational approaches share a focus on medication adherence and compliance, detecting early signs and seeking help.¹²⁰

4.3.6 RECOMMENDATIONS ON PSYCHOSOCIAL INTERVENTIONS

B Evidence based psychosocial interventions should be available to patients in addition to pharmacological maintenance treatment, especially if complete or continued remission cannot be achieved.

5 Reproductive health issues

Bipolar affective disorder is often managed with long term prophylactic medication, which may have implications for women who wish to plan a family. The main risks associated with psychotropic drugs in later pregnancy are neonatal toxicity or withdrawal syndrome following delivery and the possibility of a long term impact on the infant's neurodevelopment.¹²¹ Similar concerns exist for breast feeding and most psychotropic drugs are not licensed for use during pregnancy and lactation.¹²² Careful consideration should be given to the risks and benefits of prescribing psychotropic medication at such times.

Decisions may have to be made about commencing psychotropic drugs during pregnancy if a woman becomes ill, or more commonly, stopping medication if a woman finds that she is pregnant. In an unplanned pregnancy inadvertent exposure to psychotropic medication requires advice on the need for further investigation and possible therapeutic termination of pregnancy.

The relapse of bipolar affective disorder following earlier lithium discontinuation is greatly accelerated compared with the steady attrition to illness in non-postnatal women.¹²³ The early postnatal period also poses a particular risk for affective psychotic illness.¹²⁴

- Re-establishing prophylactic treatment should be considered after delivery in women who have discontinued treatment during pregnancy.

Much of the evidence for risk associated with drug treatments is based on case reports, case series and clinicians' reports to drug companies and regulatory authorities. Evidence is scant for newer agents and for long term developmental risk. The assumption has been made that the fetus and newborn are at least as susceptible to side effects as adults, as enzyme systems needed to metabolise the drugs are still immature.

5.1 FERTILITY

No evidence was identified linking bipolar affective disorder and the medications used with an effect on male fertility. Many psychotropic drugs interfere with sexual drive and function, so that there may be an indirect effect on fertility. Dopamine blocking drugs, such as many antipsychotic as well as some antidepressant drugs reduce female fertility by increasing prolactin levels and inhibiting menstrual periods.¹²⁵

5.2 CONTRACEPTION

5.2.1 COMBINED ORAL CONTRACEPTION (COC)

Women taking drugs which induce hepatic enzymes (eg carbamazepine) are at increased risk of breakthrough bleeding and contraceptive failure, estimated at up to seven pregnancies per 100 woman years.¹²⁶⁻¹²⁸

- D** The dose of the combined oral contraceptive should be adjusted accordingly when given with an enzyme-inducing drug
- D** Women should be warned that the efficacy of the COC is reduced
- D** Barrier methods of contraception should also be used for maximal contraceptive effect.

2-4

5.2.2 PROGESTOGEN-ONLY CONTRACEPTION

Hepatic enzyme-inducing drugs increase progestogen metabolism so that the efficacy of the progestogen-only oral contraceptive cannot be guaranteed. Medroxyprogesterone (Depo-Provera) can be used with enzyme-inducing drugs but the efficacy may be reduced after ten weeks. Implants of progestogen are not effective if given with enzyme-inducing drugs.¹²⁹

4

- D** The progestogen-only oral contraceptive is not recommended for women taking enzyme-inducing drugs.
- D** Depot injections of progesterone may be used with enzyme-inducing drugs if given every 10 weeks.
- D** Progesterone implants are not suitable for women taking enzyme-inducing drugs.

5.3 PRECONCEPTION COUNSELLING

Preconception counselling is important for all women of childbearing age and should generally cover issues such as smoking, alcohol intake, nutrition (especially folic acid), rubella titres, HIV and hepatitis B status. Specific issues that should be discussed with a woman with a diagnosis of bipolar affective disorder include:

- risks of bipolar affective disorder to the pregnancy, these include the risks to physical health associated with depression
- risks associated with the drugs used to treat bipolar affective disorder, especially lithium and anticonvulsant drugs (see section 5.4)
- use of folic acid to prevent neural tube defects (see section 5.4.1)¹³⁰
- monitoring of the illness - this may need to be increased to provide additional reassurance to the patient and also to detect early relapse
- risk of relapse during pregnancy. This is increased if lithium is discontinued but there is little difference between pregnant and non-pregnant women (52% vs. 58%). The rates for depression or dysphoria are higher (63% vs. 38%)¹²³
- risk of relapse post pregnancy. If lithium has been stopped, there is an eight-fold increase in admission rates in the first month post-partum and a two-fold increase in admission rates between months two and 12¹²¹
- lifetime risk of bipolar affective disorder for the child (see section 2.3)
- postnatal issues including breastfeeding, postnatal withdrawal from psychotropic drugs and potential long term consequences (see section 5.5).

A multidisciplinary approach is required. This will normally be led by the primary healthcare team and would include midwifery and specialist health visiting support. If necessary, access to the mental health team and to specialist obstetric advice should be available. Clinicians may wish to see patients more often during pregnancy to monitor both the mother and the fetus.

- An integrated multidisciplinary care protocol tailored to the special needs of women with bipolar affective disorder should be offered to women before, during and after pregnancy.

5.4 DRUGS IN PREGNANCY

- Clinicians should check with an up-to-date source of information before prescribing in pregnancy, eg local NHS medicines information departments, the British National Formulary¹³⁰ or directly with manufacturers' databases.
 - Information on drugs in pregnancy can also be obtained from the National Teratology Information Service (NTIS; Tel: 0191 2321525, www.spib.acl.co.uk).
- Possible effects on the unborn child should be discussed with a mother who requires acute and maintenance treatment of bipolar affective disorders. Risks should be weighed up against possible benefits.

5.4.1 ANTICONVULSANT DRUGS (ACDs)

Major and minor fetal malformations occur more commonly in infants exposed to the antiepileptic antimanic drugs (ACDs) carbamazepine, valproate and lamotrigine during pregnancy.¹³¹⁻¹³⁴ The overall risk of major fetal malformation in any pregnancy of approximately 2% is increased two to three-fold in women taking a single ACD. The relative risk is higher with valproate than carbamazepine or lamotrigine.¹³⁵ There is no reason to assume a different risk for semisodium valproate. (see also NICE Technology Appraisal Guidance 76: Epilepsy (adults) – newer drugs).¹³⁶ 2+

The most common major malformations associated with fetal exposure to established ACDs are neural tube defects (valproate 3%, carbamazepine 1%), orofacial defects, congenital heart abnormalities and hypospadias.¹³² The risk of minor malformations including hypertelorism, epicanthic folds and digital hypoplasia is increased with ACD therapy in pregnancy.¹³³ 2+
4

“Fetal anticonvulsant syndromes” comprising typical dysmorphic craniofacial appearances and a variety of musculoskeletal abnormalities have been described in association with ACD treatment in pregnancy.^{137,138} Although individual drugs have been associated with specific patterns, there is overlap between them and genetic factors may influence susceptibility.¹³⁹ 3
4

It is not clear whether or not ACDs taken during pregnancy affect a child’s intellectual development but concerns about such effects of valproate have been raised.^{140,141} There is increasing evidence of neurodevelopmental abnormalities of children whose mothers were treated with sodium valproate during pregnancy.¹⁴² 3
2+

Several ACDs, including carbamazepine, are folate antagonists. Folic acid supplements are recommended for women on ACDs from before conception at least to the end of the first trimester.¹⁴³ 2+

There is insufficient evidence on which to base advice about the risks in pregnancy of most of the newer ACDs (gabapentin, levetiracetam, tiagabine, topiramate, vigabatrin). Current data on lamotrigine show a malformation rate of up to 8%.¹⁴⁴

C All women on antiepileptic drugs as mood stabilisers should be prescribed a daily dose of 5 mg folic acid from preconception at least until the end of the first trimester.

D Valproate should be avoided as a mood stabiliser in pregnancy.

The risks of antiepileptic drugs used as mood stabilisers should be discussed with the mother before pregnancy.

Folic acid prophylaxis can usefully be prescribed in planned pregnancies from stop of contraception to completion of pregnancy.

5.4.2 LITHIUM

Lithium is regularly used on a maintenance basis in the prevention of relapse of bipolar affective disorder. Such a relapse is more likely to occur following childbirth and when lithium is withdrawn (see section 5.3).¹²³ 2+

Current practice for women with bipolar disorder who plan to or become pregnant is variable. Lithium treatment can be discontinued with close monitoring or prescription of antipsychotic medication or treatment may be maintained throughout pregnancy when the risk of relapse is significant.

Earlier studies of the use of lithium in pregnancy suggested that the risk of major fetal malformations, in particular Ebstein's anomaly, was increased by exposure in early pregnancy.¹⁴⁵ More recent evidence, based on prospective studies, suggests that this risk may have been overestimated and that the risk to the mother and child of lithium withdrawal may have been underestimated.¹⁴⁵

2+

C

- **Women with severe bipolar disorder, who are maintained on lithium, can be continued on lithium during pregnancy if clinically indicated.**
- **The serum levels of women who are maintained on lithium therapy during pregnancy should be carefully monitored. Detailed fetal ultrasound scanning should be offered.**

☑

Women with bipolar disorder maintained on lithium should receive specialist supervision from an obstetrician and a psychiatrist during pregnancy.

☑

Where possible, the risks of lithium to the fetus and the effects of lithium withdrawal on the mother should be discussed before pregnancy.

5.4.3 BENZODIAZEPINES

Case control studies have shown that exposure to benzodiazepines in early pregnancy may increase the risk of major malformations, particularly oral cleft, in the fetus.¹⁴⁶

2+

B

Benzodiazepines should be avoided in the first trimester of pregnancy.

5.4.4 NEW ANTIPSYCHOTIC DRUGS

As newer antipsychotic drugs or clozapine replace the older antipsychotic drugs in acute mania, the risk of prescribing for pregnant women may increase.¹⁴⁷ Newer ("atypical") antipsychotic drugs have not been prescribed extensively and the evidence base for their safe use in pregnancy is small.

5.4.5 ESTABLISHED ANTIPSYCHOTIC DRUGS

There is extensive experience of prescribing older antipsychotic drugs during pregnancy, with no published evidence of teratogenic effects. Extrapyramidal effects in neonates have been occasionally reported. Given this, and the consequent need for prenatal dose reduction, prescription should transfer from depot intramuscular to oral preparations.¹³⁰

☑

Older antipsychotic drugs should be prescribed as oral preparations during pregnancy.

5.4.6 ANTIDEPRESSANT DRUGS

There is extensive experience of using tricyclic antidepressants (TCAs) and increasing experience of serotonin re-uptake inhibitor (SRI) antidepressants (particularly fluoxetine) in pregnancy.¹⁴⁸ No excess complications have been reported, although there are reports of postnatal toxicity with TCAs and withdrawal symptoms in the neonate with SRIs. The use of newer antidepressant drugs, such as escitalopram, venlafaxine, reboxetine and mirtazapine cannot be considered as safe during pregnancy.

5.5 DRUG TREATMENT AND LACTATION

Women who require psychotropic medication following childbirth are likely to be discouraged from breast feeding because of the risks to the infant. The evidence base for this is limited due to the small number of breastfeeding women who have been exposed to any specific drug and the absence of a systematic approach to monitoring and registering information about the use of psychotropic medication in breastfeeding women. Clinicians are advised to check with an up to date source of information before prescribing to breastfeeding women, such as local NHS medicines information departments, the British National Formulary¹³⁰ or directly with the manufacturers' databases.

5.5.1 LITHIUM

Lithium is excreted in breast milk at a level of approximately 40% of maternal serum level. Lithium toxicity has been described in a breastfed infant and lithium is known to impair thyroid and renal function in adults.^{149,150}

3

D Mothers taking lithium should be encouraged to avoid breast feeding, particularly if the infant is not full-term and healthy. If a decision is made to proceed, close monitoring of the infant, including serum lithium levels, should be undertaken.

5.5.2 ANTICONVULSANT DRUGS

Sodium valproate is excreted in breast milk in low levels and infant serum levels are between one and two per cent of the maternal serum level. No adverse clinical effects have been noted in breastfed children when mothers are taking sodium valproate.¹⁵¹

2

Carbamazepine is excreted into breast milk in significant quantities and levels of carbamazepine in infant serum ranges from 6% to 65% of maternal serum levels.¹⁵⁰

3

Infants of breastfeeding women taking either valproate or carbamazepine should be observed for signs of toxicity.

5.5.3 OTHER PSYCHOTROPIC MEDICATION

Benzodiazepines are excreted in breast milk.^{122,152}

4

D New prescriptions for benzodiazepines should be avoided in breastfeeding mothers.

Note: this recommendation does not cover drug dependence, where breast feeding may be beneficial if the infant has been exposed to benzodiazepines in utero.

There is little evidence on the new atypical antipsychotic drugs.^{122,153} Other antidepressant drugs including moclobemide,^{154,155} venlafaxine,¹⁵⁶ and nefazodone¹⁵⁷ are all excreted in breast milk.

3

Although all forms of antipsychotic medication are excreted in breast milk there is no evidence to date to suggest that breastfed infants are at risk of toxicity or impaired development.^{121,122,152,158,159}

If a breastfeeding mother is taking psychotropic medication, infant development should be monitored and a careful assessment of the risks and benefits of prescribing at this time should be made.

6 Substance misuse

Comorbidity of affective disorders with drug and alcohol abuse is an ill-researched area, partly because the assessment of treatment invariably excludes patients with such disorders.

6.1 ALCOHOL AND SUBSTANCE MISUSE

Evidence from a cohort study demonstrates the high lifetime rates of alcohol and drug misuse in patients with bipolar affective disorder.¹⁶⁰ Among the 392 participants rates of substance abuse were high, with a 48.5% rate for lifetime alcohol abuse, a 43.9% rate for lifetime drug abuse and a 59.4% rate for lifetime drug or alcohol abuse. Rates of active substance abuse during the observed episodes were also notable with 28.6% of the cohort actively abusing alcohol, 28.6% actively abusing one or more drugs and 39.3% actively abusing either drugs or alcohol. Current and lifetime substance abuse were more common among men than among women. No differences in any of the substance abuse rates were noted between the patients with pure and the patients with mixed manic subtypes. No evidence was identified on the efficacy of interventions to treat alcohol and or drug misuse problems in patients with bipolar affective disorder.

2+

6.1.1 CARE PROGRAMME APPROACH

In 1992 a Scottish Office circular introduced the “Care Programme Approach” (CPA) for people with a mental illness in the care of health boards and local social work authorities.¹⁶¹ The aim of CPA is to ensure that individuals with severe and enduring mental illness, who also have complex health and social needs, receive continuing and coordinated care and supervision. This should incorporate appropriate packages of services and accommodation.

- Patients with bipolar affective disorder and a coexisting drug and or alcohol problem may be usefully managed under the Care Programme Approach.

7 Suicide prevention

The risk of suicide is increased in patients with bipolar illness. Estimates range from mortality ratios of 12 to 22, standardised to age of admission and time of follow up, or a lifetime risk of 8-20%.¹⁶²⁻¹⁶⁴ Bipolar affective disorder, as with other psychiatric diagnoses, is an important risk factor and predictor of suicide. It is not known whether symptom removal can effectively reduce suicide risk.

Suicide and attempted suicide have been explored in observational studies, with published evidence for reduced mortality during long term lithium treatment,¹⁶⁵⁻¹⁶⁹ for increased mortality after discontinuation of lithium^{168,170-173} and for lower mortality in patients treated with lithium compared to patients treated with carbamazepine and amitriptyline.¹⁷⁴ Suicides in patients with bipolar illness appear to be associated with no lithium treatment, non-compliance and inappropriate treatment.¹⁷⁵⁻¹⁷⁷ The greater intensity of follow up in lithium clinics (including blood tests and supportive psychotherapy) is a possible confounder in studies examining effect of lithium on suicide frequency. The efficacy of other suicide prevention strategies, such as antidepressant medication and psychosocial treatment, has been difficult to prove in studies with small sample sizes and patient selection bias.¹⁷⁸

2+

D Acute and maintenance lithium treatment of patients with bipolar affective disorders should be optimised to make every effort to minimise the risk of suicide.

8 Implementation and audit

8.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of local NHS organisations and is an essential part of clinical governance. It is acknowledged that not every guideline can be implemented immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and general practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit. Implementing the new general practice contract will provide opportunities to introduce such elements of good practice.

8.2 KEY POINTS FOR AUDIT

- Lithium treatment in bipolar illness should be standardised and audited. Audit could be facilitated by central lithium registers within tertiary services or by general practice registers that combine prescribing records with regular clinical and laboratory assessment. This has been partially addressed by the quality and outcome remit of the new general medical services (GMS) contract
- Continuous pharmacy audit should be used to monitor prescriptions of the various preparations of lithium and the different salts of valproic acid. A coherent policy should be introduced locally and preferably nationally to use unique names. The guideline development group recommends the use of brand names for lithium and semisodium or sodium valproate, respectively
- The availability and patient acceptability of psychosocial interventions for bipolar affective disorder patients should be audited
- A national needs assessment of people with bipolar affective disorder should be established along the lines of the national audit for schizophrenia. This should include regular physical check ups for patients to identify any complications, developing risk factors or other illnesses.

8.3 RECOMMENDATIONS FOR RESEARCH

The following areas for further research were identified by the guideline development group:

- efficacy of valproic acid salts and other antimanic agents in the prophylaxis of bipolar affective disorder
- evidence for early intervention and its effect on outcome
- screening, diagnosis and treatment of patients with bipolar II disorder
- treatment of patients with bipolar depression
- interventions in specific subgroups, such as the elderly, the young and people with learning disabilities
- simple psychosocial interventions to identify the active component(s) of such treatments, eg self management
- interactions of alcohol and substance misuse with bipolar affective disorder and the consequences for treatment
- service needs of patients with bipolar disorder
- a national database to define the relative risk of psychotropic medications in pregnancy.

8.4 ECONOMIC AND RESOURCE IMPLICATIONS

8.4.1 ECONOMICS OF ACUTE TREATMENT

Limited good quality economics studies were found on the relative cost effectiveness of treatments for acute mania. One cost-consequence study from the USA found that over a 12-week period, treatment with semisodium valproate or olanzapine produced similar clinical outcomes but showed no significant differences in total costs of care.¹⁷⁹ A NICE technology appraisal examining the use of olanzapine and semisodium valproate for acute mania concluded that no distinction could be made between the two drugs on cost effectiveness grounds.¹⁸⁰ This evidence would accord with the recommendation given in section 3.1.8 of the guideline. Two other studies were found relating to acute treatment but the applicability of the findings in each case was limited by poor quality methodology.^{181,182} No cost effectiveness studies were found relating to the treatment of acute bipolar depression in patients with a history of mania.

8.4.2 ECONOMICS OF MAINTENANCE TREATMENT

No cost-effectiveness studies were found relating to pharmacological treatments for relapse prevention. No full economic evaluations were found on psychosocial interventions to prevent relapse, but several clinical trials on such interventions did report information on resource use. Two studies concluded that cognitive therapy produced improvements in symptoms and functioning compared to waiting list control patients, in addition to reductions in hospital admissions.¹⁰⁸ Using psychologists to train individuals to recognise early symptoms of relapse has also been shown to be effective in reducing manic relapses (but not depressive relapses) but, contrary to the findings above, this was not associated with significant reductions in inpatient stays, outpatient visits or community contacts.¹⁰⁹

8.4.3 RESOURCE IMPLICATIONS

The guideline group examined each recommendation to identify those that would require additional resources to ensure implementation. Many of the recommendations were judged to be resource-neutral but several were noted as having considerable cost implications.

The recommendation made under section 3.1.8 states that oral administration of an anti-psychotic or valproate should be considered for acute manic episodes. It was identified that given current practice in Scotland, for some patients this could result in a change from treatment with sodium valproate (unlicensed for this indication but commonly used) to semisodium valproate. The exact numbers and geographical distribution of such patients will vary, but on the basis of average doses, this could cost an additional £1 to £2.60 per patient per day.¹³⁰

The other major resource implication that the group identified was access to psychosocial treatments. Currently such services are extremely patchy across Scotland. To implement this recommendation would require additional investment in the training of existing health professionals and also investment in the number of suitably qualified therapists available to deliver the treatments. It was noted that the supply of suitable trainers could also be a constraining factor on implementation.

9 Information for discussion with patients and carers

9.1 NOTES FOR DISCUSSION WITH PATIENTS AND CARERS

To broaden the base of patient and carers'* involvement in the development of the guideline a meeting was held with seven patients and six carers from different Scottish regions. The following points summarise the issues that they found important at the different stages of their care. This list is by no means complete, or unbiased, but it may help to guide the development and improvement of local information materials and protocols.

9.1.1 DIAGNOSIS

Patients and carers appreciated:

- a clear explanation of the time and complexity involved in making a diagnosis of bipolar affective disorder
- information about the non-medical implications of bipolar affective disorder, for example, effects on occupation and other aspects of patients' personal life (eg driving).

Patients would like:

- active involvement in the diagnostic process
- information on symptoms and possible treatment options (in a format tailored to the individual patient)
- this may require more time for consultations or even discussion sessions, the opportunity to meet with health professionals, especially after being detained, and clear written information to back up verbal information.

Carers like:

- to be involved in the diagnostic process
- to be given information on what to do when their relative/friend is ill for the first time
- practical information about risk prevention and advice on legal issues.

General points:

- both patients and carers felt that increased awareness of bipolar affective disorder and its symptoms was needed amongst health professionals
- they felt that a reduction in stigma of the diagnosis, would encourage acceptance and more effective self management.

* The term carer has been used here to describe family members, partners or close friends, whom the patient wants to be involved in his or her care.

9.1.2 TREATMENT

Patients and carers appreciated:

- the 'excellent' support they received from voluntary sector agencies and from community psychiatric nurses (CPNs).

Patients would like more:

- information from GPs
- improved information-giving by hospital psychiatrists and other medical members of staff
- information on legal and social/economic aspects of treatment
- more information on medication (before and after prescription) including side effects of treatment
- information on the effects of possible contraindications to over-the-counter medications (eg cold and flu remedies), alcohol and illegal drugs
- support in 'managing' medication levels after recovery
- information on and access to psychological therapies, complementary therapies and local support
- advice on how to complement medical treatment with lifestyle choices and make compromises
- advice on keeping mood charts, signs to look out for, information on blood monitoring, driving restrictions, travel insurance, 'triggers' to watch out for, long term consequences of treatment
- information on Advance Statements
- information on hospital discharge arrangements, local support agencies and emergency contact information.

Carers wanted:

- more information on patient choice, the pros and cons of treatment options and the expected lengths of treatment
- information on lithium withdrawal and relapse
- information on advocacy, data protection issues and human rights
- to continue to be involved in treatment plans
- advice on how to communicate with other family members
- advice on how to recognise early signs of relapse and avoid stressful 'triggers' in everyday life.

General points:

- the use of Advance Statements with people with bipolar disorders should be actively promoted as a means of improving self insight, strengthening and defining the doctor-patient relationship and facilitating the least restrictive alternative in compulsory treatment
- users and carers should be truly involved in decision making processes in relation to their own care and treatment options
- patients require timely and efficient access to the most appropriate service at any given time eg crisis services, inpatient facilities, psychological services and other voluntary sector support services
- greater availability of respite care facilities
- increased availability of life skills coaching to facilitate maximum participation, inclusion and productivity when well
- better awareness on side effects and toxicity awareness, for patients and GPs. Included in this is the need for users and carers to be aware of the importance of regular blood checks if required
- patients should be involved, where possible, in discussions on treatment options, introducing the element of choice and informed decision making

9.2 SOURCES OF FURTHER INFORMATION AND SUPPORT FOR PATIENTS AND CARERS

Bipolar Fellowship Scotland

Studio 1016, Mile End Mill, Abbey Mill Business Centre, Seedhill Road, Paisley PA1 1TJ
Tel: 0141 560 2050
www.bipolarscotland.org.uk

Provides information and advice to anyone with an interest in bipolar affective disorder. Network of self help groups throughout Scotland.

CarersNet

www.carers.net

The official website of the Coalition of Carers in Scotland - an information network designed for carers, carer groups and organisations, and for people working with carers.

Carers Online

www.carersonline.org.uk

A partnership website that provides carers, those supporting them and others with national and local information.

Depression Alliance Scotland

3 Grosvenor Gardens, Edinburgh EH12 5JU
Tel: 0131 467 3050
www.depressionalliance.org

Information and support for people in Scotland with depression.

Highland User Group Highland Community Care Forum

Highland House, 20 Longman Road, Inverness IV1 1RY
Tel: 01464 718817
www.hug.uk.net

MDF Aberdeen

87 Holburn Street, Aberdeen AB10 6BQ
Tel: 01224 590435
www.mdf-aberdeen.com

MDF – The Bipolar Organisation

UK Head Office, Castle Works, 21 St George's Road, London SE1 6ES
Tel: 0845 340 540
www.mdf.org.uk

Information and support for people with bipolar affective disorder in the UK. Runs self management training and has a comprehensive range of publications on a range of topics, including a guide to medications.

National Schizophrenia Fellowship (Scotland)

Claremont House, 130 East Claremont Street, Edinburgh EH7 4LB
Tel: 0131 557 8969
www.nsfscot.org.uk

Information and support on severe mental health problems, especially schizophrenia. Offers support to carers, and has many services across Scotland. Provide a leaflet entitled "Mental illness in your family" which includes a section on bipolar disorder.

Scottish Association for Mental Health (SAMH)

Cumbræ House, 15 Carlton Court Glasgow G5 9JP
Tel: 0141 568 7000
email: enquire@samh.org.uk • www.samh.org.uk

Information and advice on all aspects of mental health, Monday to Friday 2-4.30pm.

'see me'

Tel: 0131 624 8945

www.seemescotland.org

National campaign highlighting, and fighting, the stigma of mental ill health. Encourages people to tell their stories of stigma, monitors and responds to episodes of stigma and links anti-stigma work Scotland wide.

Youngmindswww.youngminds.org.uk

Provide a leaflet entitled "Mental illness in your family" which includes a section on bipolar disorder.

9.2.1 NATIONAL TELEPHONE HELPLINES

Breathing Space

Tel: 0800 83 85 87

www.breathingspacescotland.org.uk

A free, confidential phone-line for men. The phone-line is open from early evening to 2 am. Breathing Space advisors can offer advice and suggest local people who can help with specific problems. Calls do not appear on the phone bill.

Samaritans

Tel: 08457 90 90 90

www.samaritans.org.uk

Available 24 hours a day to provide confidential emotional support for people who are experiencing feelings of distress or despair.

Saneline

Tel: 08457 67 80 00

www.sane.org.uk

9.2.2 LEGAL ADVICE

Adults with Incapacity (Scotland) Act 2000www.scotland-legislation.hmso.gov.uk/legislation/scotland/acts2000/20000004.htm**Driver and Vehicle Licensing Agency (DVLA) Medical Rules**www.dvla.gov.uk/drivers/dmed1.htm**Mental Health (Care and Treatment) (Scotland) Act 2003**www.scotland-legislation.hmso.gov.uk/legislation/scotland/acts2003/20030013.htm**Mental Welfare Commission for Scotland**

Argyle House, 3 Lady Lawson Street, Edinburgh, EH3 9SH

Tel: 0131 222 6111

email: enquiries@mwscot.org.uk • www.mwscot.org.uk

The Commission has the responsibility for protecting the welfare of people with mental disorder in Scotland, and is accountable to the Scottish Parliament.

Office of the Public Guardianwww.publicguardian-scotland.gov.uk/html/welcome.htm

10 Development of the guideline

10.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practicing clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50; A Guideline Developer’s Handbook”, available at www.sign.ac.uk

10.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Klaus Ebmeier <i>Chair</i>	<i>Professor of Psychiatry, University of Edinburgh</i>
Dr Benjamin Baig <i>Secretary</i>	<i>Senior House Officer, Royal Edinburgh Hospital</i>
Ms Ailsa Brown	<i>Health Economist, Greater Glasgow Health Board</i>
Dr Jonathan Cavanagh	<i>Senior Lecturer in Psychiatry, Gartnavel Hospital, Glasgow</i>
Dr Stella Clark	<i>Acting Medical Director, Fife Primary Care NHS Trust</i>
Professor Kate Davidson	<i>Director of Glasgow Institute of Psychosocial Interventions, University of Glasgow</i>
Ms Nadine Dougall	<i>Research Fellow, University of Edinburgh</i>
Mrs Karen Fraser	<i>Principal Pharmacist - Mental Health, Ailsa Hospital, Ayr</i>
Dr Kenneth Lawton	<i>General Practitioner, Aberdeen</i>
Ms Fiona Mitchell	<i>Community Psychiatric Nurse, Westbank Clinic, Falkirk</i>
Dr Anne Nightingale	<i>Consultant Psychotherapist, Lansdowne Clinic, Glasgow</i>
Mr Chris O’Sullivan	<i>Lay representative, Edinburgh</i>
Professor Mick Power	<i>Clinical Psychology Course Director, University of Edinburgh</i>
Professor Ian Reid	<i>Professor of Psychiatry, Aberdeen University</i>
Mr Duncan Service	<i>Senior Information Officer, SIGN Executive</i>
Mrs Marion Shawcross	<i>Social Work Officer, The Mental Welfare Commission for Scotland, Edinburgh</i>
Ms Ailsa Stein	<i>Programme Manager, SIGN Executive</i>
Ms Joanne Topalian	<i>Programme Manager, SIGN Executive</i>
Dr Alan Wade	<i>General Practitioner, Glasgow</i>
Mr Laurence Wilson	<i>Lay representative, Glasgow</i>

The guideline group is also very grateful for the work done by the members of the SIGN “epilepsy in adults” and “postnatal depression and puerperal psychosis” guideline groups.

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive.

10.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group. Literature searches were initially conducted in Medline, Embase, Cinahl, Psychinfo and the Cochrane Library using the year range 1990-2003. The literature search was updated with new material during the course of the guideline development process. A final update search was performed in April 2004. Key websites on the Internet were also used, such as the National Guidelines Clearinghouse. These searches were supplemented by reference lists of relevant papers and group members' own files. The Medline version of the main strategies can be found on the SIGN website. The work of the guideline groups for postnatal depression and puerperal psychosis (Guideline 60) and diagnosis and management of epilepsy in adults (Guideline 70) formed the basis of some of the recommendations in section 5.

10.4 CONSULTATION AND PEER REVIEW

10.4.1 NATIONAL OPEN MEETING

The national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held in November 2003 and was attended by all of the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for one month to allow those unable to attend the meeting to contribute to the development of the guideline.

10.4.2 SPECIALIST REVIEW

The guideline was also reviewed in draft form by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to this guideline.

Dr Ian Anderson	<i>Consultant Psychiatrist, Manchester Royal Infirmary</i>
Dr Fiona Bisset	<i>Consultant in Public Health Medicine, Scottish Executive, Edinburgh</i>
Mr Bill Cook	<i>Lead Officer, Social Work Headquarters, Inverness</i>
Mrs Pat Dawson	<i>Head of Policy and Communications, RCN Scotland</i>
Mr Rodney Elgie	<i>President, Global Alliance of Mental Illness Advocacy Networks, Tonbridge, Kent</i>
Professor Kay R Jamison	<i>Professor of Psychiatry, Johns Hopkins University, Baltimore, USA</i>
Dr Mary Hepburn	<i>Consultant Obstetrician, Princess Royal Maternity Hospital, Glasgow</i>
Dr Daphne Keen	<i>Chair, Psychiatry and Psychology Specialty Group, Royal College of Paediatrics and Child Health, London</i>
Dr Patricia McElhatton	<i>Consultant Teratologist, Head of NTIS and Lecturer in Reproductive Toxicology, The National Teratology Information Service, Newcastle upon Tyne</i>
Dr Gerry McPartlin	<i>General Practitioner, Edinburgh</i>
Dr Sandy Reid	<i>General Practitioner, Edinburgh</i>
Ms Michelle Rowlett	<i>Chief Executive, Manic Depression Fellowship, London</i>
Mr Steve Spence	<i>Primary Mental Health Worker, Lawson Memorial Hospital, Sutherland</i>
Professor Alan Young	<i>Professor of Psychiatry, University of Newcastle</i>
Dr Eduard Vieta	<i>Director of Research, Department of Psychiatry, University of Barcelona, Spain</i>
Mr Andrew Walker	<i>Pharmacy Services Manager, Dykebar Hospital, Paisley</i>

8.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Dr David Alexander	<i>General Practitioner, Fife</i>
Dr Keith Brown	<i>Consultant Psychiatrist, Forth Valley Primary Care Trust</i>
Professor Derek W Johnston	<i>Professor of Psychology, University of Aberdeen</i>
Professor Gordon Lowe	<i>Chair of SIGN; Co-Editor</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>

Abbreviations and glossary

ACDs	Anticonvulsant drugs
Advance Statements	An ‘advance statement’ is a way of giving details, when a person is well enough to do so, about how they would like to be treated if they ever become too ill to make decisions about their care or treatment. This could include specifying a preference to have a particular treatment which has been effective before, or a wish not to have a treatment where side effects have been problematic. The Mental Health (Care and Treatment) Scotland Act 2003 gives advance statements a legal footing for the first time. It lays down specific criteria for the preparation and application of these statements as part of care for both formal and informal patients.
Bipolar I	Bipolar affective disorder with manic (and depressive) episodes
Bipolar II	Bipolar affective disorder only with hypomanic (and depressive) episodes
BNF	British National Formulary: http://bnf.org
BPRS	Brief Psychiatric Rating Scale
CARS-M	Clinician –Administered Rating Scale for Mania
CBT	Cognitive behavioural therapy
CI	Confidence interval
COC	Combined oral contraception
CPA	Care programme approach
CPN	Community psychiatric nurse
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4 th Edition
Dysphoria	Mild form of depression
Ebstein’s anomaly	Also called Ebstein’s malformation. A heart defect in which the tricuspid valve is abnormally formed. The tricuspid valve normally has three “flaps”. In Ebstein’s anomaly, one or two of the three flaps are stuck to the wall of the heart and don’t move normally. There may be a hole in the wall between the atria, the heart’s two upper chambers.
ECT	Electroconvulsive treatment
Euthymic	Neither depressed nor hypomanic or manic, normal mood.
Extrapyramidal	Type of neurological symptoms, common in Parkinsonism
FFT	Family focused therapy
GMS	General medical services
GP	General practitioner
Hypomania	Elated mood not leading to admission to hospital
ICD-10	International Classification of Diseases version 10
Informed consent	Consent obtained freely without coercion, after appropriate and understandable information has been given and questions answered.
IPSRT	Interpersonal and social rhythm therapy

Mania	More severely elated mood often requiring admission to hospital
MDQ	Mood Disorder Questionnaire
MINI	Mini International Neuropsychiatric Inventory
NICE	National Institute for Clinical Excellence
NTIS	National Teratology Information Service
PSE	Present State Examination
PSQ	PSYCHOSIS Screening Questionnaire
RCT	Randomised Controlled Trial
RR	Relative risk
SCID	Scheduled Clinical Interview for DSM
SIGN	Scottish Intercollegiate Guidelines Network
SRI	Serotonin re-uptake inhibitor
TCAs	Tricyclic antidepressants
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

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Update to printed guideline

8 Jul 2005

Section 9.2

Contact details for MDF Aberdeen added

MDF Aberdeen
87 Holburn Street, Aberdeen AB10 6BQ
Tel: 01224 590435
www.mdf-aberdeen.com

▶ SOURCES OF FURTHER INFORMATION

Bipolar Fellowship Scotland
Studio 1016, Mile End Mill, Abbey Mill Business Centre,
Seedhill Road, Paisley PA1 1TJ
Tel: 0141 560 2050
www.bipolar-scotland.org.uk

Breathing Space
Tel: 0800 83 85 87
www.breathingspacescotland.org.uk

Depression Alliance Scotland
3 Grosvenor Gardens, Edinburgh, EH12 5JU
Tel: 0131 467 3050
www.depressionalliance.org

MDF – The Bipolar Organisation
UK Head Office, Castle Works, 21 St George's Road, London SE1 6ES
Tel: 0845 340 540
www.mdf.org.uk

▶ SOURCES OF FURTHER INFORMATION

National Schizophrenia Fellowship (Scotland)
Claremont House, 130 East Claremont Street, Edinburgh EH7 4LB
Tel: 0131 557 8969
www.nsfscot.org.uk

Samaritans
Tel: 08457 90 90 90
www.samaritans.org.uk

Saneline
Tel: 08457 67 80 00
www.sane.org.uk

Scottish Association for Mental Health (SAMH)
Cunbrae House, 15 Carlton Court, Glasgow G5 9JP
Tel: 0141 568 7000
email: enquire@samh.org.uk • www.samh.org.uk

▶ LEGISLATION

Adults with Incapacity (Scotland) Act 2000
www.scotland-legislation.hmso.gov.uk/legislation/scotland/acts2000/20000004.htm

Driver and Vehicle Licensing Agency (DVLA) Medical Rules
www.dvla.gov.uk/drivers/dmed1.htm

Mental Health (Care and Treatment) (Scotland) Act 2003
www.scotland-legislation.hmso.gov.uk/legislation/scotland/acts2003/20030013.htm

Mental Welfare Commission for Scotland
Argyle House, 3 Lady Lawson Street, Edinburgh, EH3 9SH
Tel: 0131 222 6111
email: enquiries@mhwscot.org.uk • www.mhwscot.org.uk

Office of the Public Guardian
www.publicguardian-scotland.gov.uk/html/welcome.htm

Quick Reference Guide • Bipolar Affective Disorder

DIAGNOSIS

- ✓ Early and accurate diagnosis should be attempted to allow treatment as soon as possible after a first episode.

D A diagnosis of bipolar affective disorder should be made after clinical assessment according to DSM or ICD criteria.

- ✓ Clinicians should be aware of the instability of diagnosis during clinical review of patients with affective disorder.

SIGNS AND SYMPTOMS OF MANIA

Signs and symptoms of mania (or a manic episode) include:

- increased energy, activity, and restlessness
- excessively high, overly good, euphoric mood
- extreme irritability
- racing thoughts and talking very fast, jumping from one idea to another
- distractibility, cannot concentrate well
- little sleep needed
- unrealistic beliefs in one's abilities and powers
- poor judgement
- spending sprees
- a lasting period of behaviour that is different from usual
- increased sexual drive
- abuse of drugs, particularly cocaine, alcohol, and sleeping medications
- provocative, intrusive, or aggressive behaviour
- denial that anything is wrong.

SIGNS AND SYMPTOMS OF DEPRESSION

Signs and symptoms of depression (or a depressive episode) include:

- lasting sad, anxious, or empty mood
- feelings of hopelessness or pessimism
- feelings of guilt, worthlessness, or helplessness
- loss of interest or pleasure in activities once enjoyed, including sex
- decreased energy, a feeling of fatigue or of being slowed down
- difficulty concentrating, remembering, making decisions
- restlessness or irritability
- sleeping too much, or can't sleep
- change in appetite and/or unintended weight loss or gain
- chronic pain or other persistent bodily symptoms not caused by physical illness or injury
- thoughts of death or suicide, or suicide attempts.

ACUTE TREATMENT FOR MANIA

- Acute manic episodes should be treated with oral administration of an antipsychotic drug or semi-sodium valproate.
- Lithium can be used if immediate control of overactive or dangerous behaviour is not needed or otherwise should be used in combination with an antipsychotic.

- ✓ Intra-muscular injection of antipsychotics and/or benzodiazepines (lorazepam) should be used in emergency situations, in accordance with local protocols.

- ✓ Benzodiazepines may be used as adjunctive treatment in acute mania where sedation is a priority.

- ✓ Patients who suffer an acute manic episode whilst on maintenance treatment with an anti-manic drug should have their dose of anti-manic drug optimised. Treatment with an antipsychotic or valproic acid should be initiated as appropriate.

- ✓ Severe, treatment-resistant mania may require electro-convulsive treatment.

- ✓ Combination therapy with several anti-manic agents from different classes may be required in treatment resistant cases.

- ✓ Duration of treatment will be determined by the reduction of symptoms, the emergence of side effects and the need to provide treatment for residual symptoms and prevent relapse.

- ✓ Antidepressant drug treatment should be reduced and discontinued during an acute manic episode.

- ✓ A clear terminology should be implemented to avoid confusion in the prescription of sodium valproate and semisodium valproate, as well as the different lithium salts and preparations.

ACUTE TREATMENT FOR DEPRESSION

B An antidepressant in combination with an anti-manic drug (lithium, semisodium valproate or an antipsychotic drug), or lamotrigine is recommended for the treatment of acute bipolar depression in patients with a history of mania.

- ✓ Patients maintained on mood stabilisers who suffer a depressive episode should be started on an antidepressant after optimising their mood stabiliser.

- Interactions between serotonergic antidepressants, antipsychotic drugs and lithium and the risk of triggering mania or rapid cycling should be considered when selecting an antidepressant.

- ✓ ECT may be considered for patients with bipolar depression at high risk of suicide or self-harm.

PHARMACOLOGICAL RELAPSE PREVENTION

A Lithium is the treatment of choice for relapse prevention in bipolar affective illness.

A Lithium should be prescribed at an appropriate dose with a daily dosing regimen.

A The withdrawal of lithium should be gradual to minimise the risk of relapse.

- ✓ In general practice, lithium should be prescribed in the context of a shared care protocol to minimise side effects and toxicity.

- ✓ Before embarking on maintenance treatment with lithium patient and doctor should consider severity of the last episode, number, frequency and severity of previous episodes, personal factors, such as a wish to become pregnant or the wish to avoid sick leave from work or education.

A Carbamazepine can be used as an alternative to lithium, particularly in patients with bipolar II, or when lithium is ineffective or unacceptable.

A Lamotrigine can be used as a prophylactic in patients who have initially stabilised with lamotrigine, particularly if depressive relapse is the greater problem.

PSYCHOSOCIAL INTERVENTIONS

B Evidence based psychosocial interventions should be available to patients in addition to pharmacological maintenance treatment, especially if complete or continued remission cannot be achieved.

REPRODUCTIVE HEALTH ISSUES

D

- The dose of the combined oral contraceptive should be adjusted accordingly when given with an enzyme-inducing drug.
- Women should be warned that the efficacy of the COC is reduced.
- Barrier methods of contraception should also be used for maximal contraceptive effect.

Further information and recommendations on reproductive health issues are available in the full guideline.

SUICIDE PREVENTION

D Acute and maintenance lithium treatment of patients with bipolar affective disorders should be optimised to make every effort to minimise the risk of suicide.