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Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology

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

Key words: anticonvulsants, antidepressants, antipsychotics, bipolar disorder, CBT, depression, evidence-based guidelines, lithium, mania, mood stabilizers, treatment

Introduction

Bipolar disorder has been and remains a relatively neglected condition. This has two divergent consequences. First, there is a perception, which we broadly share, that treatment could and should be improved. Guidelines provide an opportunity to do so. Second, because of a relative dearth of high quality research, the confidence with which we can advocate particular treatments is limited. It is also an unfortunate truth that where uncertainty abounds, guidelines may proliferate.

Guidelines are systematically derived statements that are aimed at helping individual patient and clinician decisions. The principle recommendations usually apply to the *average* patient. They can be graded according to the strength of the evidence from appropriate, preferably randomized trials. Such recommendations may be expected to apply approximately 70% of the time, and so we have used expressions such as 'Clinicians *should* consider …' in the text. However, there will be occasions when adhering to such a recommendation unthinkingly could do more harm than good.

We have also recommended options. These systematically derived statements are not prescriptive. We have phrased options as 'Clinicians may' or 'Clinicians may consider …'. They recognize that implementation will depend on individual and local circumstances. Options provide a summary of up-to-date evidence and may highlight current uncertainties.

Finally, some of our recommendations may be regarded as standards of care. Standards are intended to apply rigidly. Many standards are driven by ethical consensus rather than evidence. Where standards are evidence-based, confidence and consensus must be very high, perhaps requiring that standards be adhered to > 90% of the time. We have phrased such recommendations in the imperative tense or as a directive.

This approach to making recommendations of policy is well established (Eddy, 1990). In general, we have tried to ensure that our recommendations reflect both the degree of certainty about what will happen if any given policy is followed and the extent to which the patient's and clinician's preferences are both known and consistent with the likely outcomes.

Methodology

This document is the result of an initial meeting on 24 May 2002. Brief presentations were made on key areas, with an emphasis on systematic reviews and randomized controlled trials (RCTs). This was followed by a discussion of the important issues in order to identify consensus, on the one hand, and areas of uncertainty on the other. A literature review was then assembled formally to justify the consensus points. This review was circulated to participants and other interested parties, together with recommendations and their strength based on the level of evidence. Their feedback was, as far as possible, incorporated into the final version of the guidelines.

Identification of relevant evidence

All the consensus points and the guideline recommendations can be linked to relevant evidence through the literature review. However, our methodology did not allow for a systematic review of all possible data from primary sources. Existing systematic reviews and RCTs were identified from MEDLINE and EMBASE

searches and from the Cochrane Database, as well as from previous guidelines (Sachs *et al*., 2000; American Psychiatric Association, 2002; Grunze *et al*., 2002; Suppes *et al*., 2002), cross-referencing and identification by experts in the field.

Strength of evidence and recommendations for guidelines

Categories of evidence for causal relationships (including treatment) and grading of recommendations are taken from the methodology of the North of England Evidence-Based Guideline Development Project undertaken by the Centre for Health Services Research, University of Newcastle upon Tyne and the Centre for Health Economics, University of York (Shekelle *et al*., 1999).

Evidence categories

Evidence categories are adapted from the US Agency for Health Care Policy and Research Classification (US Department of Health and Human Services, 1992). Potentially, six categories are available.

Categories of evidence relevant to specific causal relationships and treatments

Ia: Evidence from meta-analysis of RCTs
Ib: Evidence from at least one RCT
IIa: Evidence from at least one controlled study without randomization
IIb: Evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

This categorization is most appropriate to questions of causal relationships and treatments. A similar approach to observational findings is given below.

Proposed categories of evidence for observational findings and associations

I: Evidence from large representative population samples
II: Evidence from small, well designed, but not necessarily representative samples
III: Evidence from non-representative surveys, case reports
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

Recommendations are graded A to D as shown below. While it is possible to have methodologically sound (category I) evidence about an area of practice that is clinically irrelevant or has such a small effect that it is of little practical importance, in practice, the volume of the available evidence has been limited and this has scarcely been an issue. More commonly, it has been necessary to extrapolate from the available evidence or opinion. This leads to weaker levels of recommendation (B, C or D), but such recommendations may still cover key areas of practice. Where recommendations are not strictly based on systematic evidence at all, but represent an important consensus (practical or ethical), we have indicated S (standard of care), but we do not review these points in depth.

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

A particular conflict in these and other guidelines arises between existing practice and the interpretation of recent trials of new compounds. Existing practice may be accepted as clinically effective on the basis of long standing experience and/or by extension of a related proven indication. A new treatment may be supported by methodologically good trials against placebo, but lack comparator data against an accepted current treatment. We believe that responsible guidelines should highlight where this kind of dilemma is sharpest and not impose too specific a recommendation that may be premature.

Scope and target of the guidelines

The content of the guidelines is relevant for all doctors treating patients with bipolar disorder. We hope that, in most cases, these will be doctors who are specialists in psychiatry. However, we have also written the guidelines with an eye to informing general practitioners, patients and their families and health care providers with an interest in bipolar disorder.

We have emphasized our interest in evidence. However, we could not review all the relevant literature in the detail required to give a fully comprehensive text. Even distilling the evidence and summarizing points of consensus, relating mainly to medical management of bipolar disorder, does not result in a format that is particularly brief or easy to use. Accordingly, this guideline is presented in two parts. Part 1 abstracts the key *recommendations* (and some of the key points of evidence) and can inform everyday practice. Part 2 indicates all the consensus points that emerged and briefly summarizes the evidence. The structure and content are broadly, but not precisely, aligned between Parts 1 and 2.

PART 1: GUIDELINES

In making recommendations that will be of practical value to clinicians who treat patients with bipolar disorder, we stand on the consensus view of the evidence reviewed in Part 2. Clinical practice guidelines developed by other organizations have also been considered, in particular, the recently revised American Practice Guideline for the Treatment of Patients With Bipolar Disorder [American Psychiatric Association, 2002 (APA)]. We have followed the outline of the summary and synopsis of the APA guideline in making our own recommendations because our consensus group endorsed many of the recommendations made in the American document. However, the wording and emphasis is different, reflecting the variation in our use of language, our approach to clinical problems and the organization of clinical

services. We have sometimes reached different conclusions from other guidelines. Material differences in recommended practice are indicated by an asterix. These differences usually result from different weights placed on the available evidence. This is of course most likely when the evidence itself is less than compelling.

Fundamentals of patient management

- Diagnosis
- Access to services and safety
- Enhanced care

Diagnosis

Clinicians should make accurate diagnoses of hypomania, mania and mixed states (S). Consider the identification of the core symptoms of mania or depression against a check list as in DSM-IV to improve confidence in, and the reliability of diagnosis (A).

The term hypomania should be used as defined in DSM-IV, where it is confined to elated states WITHOUT significant functional impairment (S).

Bipolar symptoms such as irritability or aggression may appear, with the benefit of hindsight, to be misdiagnosed by clinicians when a patient is first seen (I). In fact, diagnosis can only be reliable after a clear-cut episode of (hypo)mania; however, in the presence of mood elevation, disturbed behaviour should not be attributed solely to personality problems or situational disturbance (B).

Bipolar patients may present with depression (I). Ask about a history of elated, excited or irritable mood of any duration in all patients with depression and about a family history of mania (S).

Anxiety disorders may be comorbid with bipolar disorder (I) and require assessment (S).

Illicit stimulant drugs may mimic manic symptoms (II). A drug-induced psychosis should wane with the clearance of the offending drug (II). L-Dopa and corticosteroids are the most common prescribed medications associated with secondary mania (I).

More commonly, drug and/or alcohol misuse is comorbid with manic or depressive mood change (I). The mood state will then significantly outlast the drugged state and a diagnosis of bipolar disorder can be made (S).

Organic conditions, such as thyroid disease, multiple sclerosis or any lesion(s) involving right-sided sub-cortical or cortical areas, may be associated with secondary mania (II) and should be considered in the differential diagnosis (S).

Access to services and the safety of the patient and others

When mania is diagnosed, always consider admission to hospital or intensive community management (S). The particular risks to the patient and others will be the result of poor judgment and associated actions in areas of work, personal relationships, alcohol/substance misuse, spending, driving and sexual activity (I).

Always try to obtain third party information if in any doubt when making a risk assessment (S).

When in a mixed state or depressed, ask every patient about suicidal ideation, intention to act on these ideas and extent of plans, means or preparation for suicide (S). Social isolation, substance misuse, psychosis (especially with command hallucinations), personality disorder, family history of suicide, recent exposure to suicide and any previous suicide attempts may all increase the risk (I).

Carefully document your decisions in formulating a care plan (S).

Enhanced care

(a) Establish and maintain a therapeutic alliance

Take responsibility for diagnosis, physical examination, investigations and explanation of the medical plan of management (S). Communicate clearly and honestly what you think (S). Take the time to listen to what is bothering the patient (S).

Very disorganized psychotic patients with bipolar disorder will have social needs that merit assertive management (B).

(b) Educate yourself and then the patient and his or her family about the disorder

Doctors, patients and carers tend to bring different experiences and beliefs to the therapeutic relationship (II) and make different estimates of future risks. Make use of evidence to address the seriousness of the illness, reluctance to give up the experience of hypomania or mania, the risk of relapse and the benefit of therapeutic engagement (D).

(c) Enhance treatment adherence

While respecting patient preferences, education about the illness after an acute manic or mixed episode should emphasize the need for medicines long-term (S).

Known tolerability of available medicines should guide prescribing: inform patients about possible side-effects and monitor their possible emergence (S). Make their reduction a priority, by lower dosing, different scheduling (e.g. prescribe all sedative medicines at bed time) and alternative formulations (B).

Consider participation in clinical trials because this can improve patient care and outcomes (A).

(d) Promote awareness of stressors, sleep disturbance and early signs of relapse, and regular patterns of activity

Sleep disruption is often the final common pathway triggering manic episodes and is also associated with depression: stressors that lead to reduced sleep may contribute to relapse (II).

Regular patterns of daily activities should be promoted (D). Identify and try to modify habitual very irregular patterns of activity, which are common in bipolar patients: consider using diaries of mood or activities (D).

Because alcohol and substance misuse are associated with a poor outcome, they require assessment, and appropriate advice and treatment (A).

Help the patient, family members and significant others to recognize signs and symptoms of manic or depressive episodes for early treatment (B).

A consistent long-term flexible alliance between the patient, the patient's family and one effective clinician is the ideal arrangement for outpatient care (S).

(e) Evaluate and manage functional impairments

Full functional recovery seldom occurs within the 12 weeks

following the remission of mood symptoms (I). Advise the patient in scheduling withdrawal from work or other responsibilities when necessary (S). Discourage major life decisions while in a depressive or manic state (S).

Patients may experience considerable difficulty performing at the level for which their education has prepared them (II). Manage patient expectations of their capacity to work (S).

Consider the needs of carers and children of patients with bipolar disorder: provide information about local or national support groups (S).

Treatment of different phases of bipolar illness

- Acute manic or mixed episode
- Acute depressive episode
- Long-term treatment
- Treatment in special situations

Prescribers should be aware of the limitations imposed by licenses for different medicines and potential safety concerns documented in product descriptions (S). Companies are currently seeking extensions to product licenses and new indications in bipolar disorder.

Product licenses are primarily designed to limit the actions of companies, *not* clinicians. Accordingly, 'off-label' prescribing of medicines is implied by some of the recommendations incorporated below. However, seek expert advice if unsure about the efficacy or safety of any individual medicine or its use in combination (S).

Acute manic or mixed episode

Choice of an initial treatment

Most patients with mania will require short-term treatment with medicine(s) in an appropriate clinical setting (Ia or Ib). No psychotherapy currently provides an alternative strategy for management.

*(a) For patients not already on long-term treatment for bipolar disorder**

For severe manic or mixed episodes, initiate oral administration of an antipsychotic or valproate because of their rapid anti-manic effect (A).

Where an agitated patient requires parenteral treatment to control behaviour without their full consent, the use of antipsychotics and benzodiazepines should follow established protocols (S). The lowest doses necessary should be employed (A). Do not escalate the dose of antipsychotic simply to obtain a *sedative* effect (S).

For less ill manic patients, lithium or carbamazepine may also be considered as a short-term treatment (A).

To promote sleep for agitated overactive patients in the short term, consider adjunctive treatment with a benzodiazepine, such as clonazepam or lorazepam (B).

Atypical antipsychotics should be considered because of their generally more favourable short-term adverse effect profile and the increasing evidence of their efficacy as anti-manic agents (A).

Treatment selection should be guided, where possible, by patient preference (S).

Antidepressants should be tapered and discontinued (B).

(b) For patients who suffer a manic or mixed episode while on long-term treatment

Long-term treatments will usually be lithium, carbamazepine or valproate (I).

If current episode is due to inadequate symptom control, ensure that the highest well-tolerated dose is offered (A). For lithium, check serum levels are within the therapeutic range; consider establishing a higher serum level within the therapeutic range (A).

Initiate an antipsychotic or valproate, as above (A)*.

Consider patient preferences established in previous illnesses or, ideally, as an advance directive (S).

In general, follow the same principles as for a first episode or an episode occurring off long-term treatment (A).

If a current episode is due to poor adherence, establish whether this is associated with actual or perceived side-effects. If so, consider a more tolerable alternative regimen. If due to lithium discontinuation because of poor adherence, and not related to tolerability, use of lithium long-term may not be indicated (B)*.

(c) If symptoms are inadequately controlled with optimized doses of the first-line medicine and/or mania is very severe, add another medicine

Consider the combination of lithium or valproate with an antipsychotic (A).

Consider clozapine in more refractory illness (B).

Electroconvulsive therapy (ECT) may be considered for manic patients who are severely ill and/or whose mania is treatment-resistant, those patients who express a preference for ECT and patients with severe mania during pregnancy (C).

(d) For psychosis during a manic or mixed episode that is not congruent with severe affective symptoms, treat with an antipsychotic

Consider atypical antipsychotics because of their generally more favourable short-term adverse effect profile (A).

(e) Discontinuation of short-term treatments

Medicines used for acute treatment may be reduced in dose and discontinued (tapering over two weeks or more) after full remission of symptoms (B). This will often occur within 3 months (I).

Any medication used for symptomatic effect (hypnotics, sedatives) should be discontinued as soon as symptoms improve (S).

Medicines shown to be effective or probably effective in relapse prevention (especially lithium and valproate) are often used for short-term treatment of mania and may be appropriately continued when long-term treatment is planned (see below).

Acute depressive episode

*Choice of an initial treatment**

(a) For patients not already on long-term treatment for bipolar disorder

Treatment with an antidepressant [e.g. Selective Serotonin Reuptake Inhibitor (SSRI)] and an anti-manic agent (e.g. lithium, valproate or an antipsychotic) together is recommended for patients with a history of mania (B). Antidepressant monotherapy is not recommended for such patients (B).

Consider adding an antipsychotic, especially when patients have psychotic symptoms (A).

Consider ECT for patients with high suicidal risk, psychosis,

severe depression during pregnancy or life-threatening inanition (A). It is unusual for ECT to be used against a patient's will, and fears about this should be allayed (S).

Where depressive symptoms are less severe, and despite limited evidence, consider initial treatment with lamotrigine, lithium or, possibly, valproate (B)*.

Clinicians and patients should be aware of the risk of mania, hypomania or rapid cycling in patients with bipolar II or bipolar spectrum disorder treated with antidepressants alone (S).

Consider interpersonal therapy and cognitive behaviour therapy when available (B).

(b) For patients who suffer a depressive episode while on long-term treatment

Ensure adequate doses of medicines and that serum levels of lithium are within the therapeutic range (B). Address current stressors, if any (B).

Ensure current choice of long-term treatments is likely to protect the patient from manic relapse (e.g. lithium, valproate, antipsychotic) (A).

If the patient fails to respond to optimization of long-term treatment, and especially if depressive symptoms are significant, initiate an antidepressant (or consider augmentation or change of antidepressant if already receiving one; see treatment-resistant depression below) (A).

*(c) Choice of antidepressant**

The limited evidence supports the efficacy of antidepressants such as the SSRIs in bipolar disorder (Ia)

There is a risk of switch to mania or mood instability during treatment for depression (I). While this will often reflect the natural history of the disorder, it may be increased by active treatment with an antidepressant (II). Antidepressants appear less likely to induce mania when added to lithium, valproate or an antipsychotic (IIa).

Tricyclic antidepressants carry a greater risk of precipitating a switch to mania than other antidepressants (Ia) and are not recommended, except for treatment-resistant patients (C).

Consider lamotrigine for bipolar depression, especially if an antidepressant has previously appeared to provoke mood instability (A).

(d) Tapered discontinuation of antidepressants may be considered after full remission of symptoms (C)

Depressive episodes that remit in bipolar disorder tend to be shorter than in unipolar disorder (I), so discontinuation may occur after as little as 12 weeks of treatment.

If treatment has been initiated with an antidepressant and an anti-manic agent *de novo* in a bipolar illness course, long-term treatment should be considered (see below) (A).

(e) Treatment-resistant depression

Relative or even marked treatment resistance may occur in depressed bipolar patients (II). Because there is so little data from trials on the treatment of bipolar patients, practice derived primarily from experience in unipolar patients is recommended (D, see BAP guideline on the use of antidepressants: Management when initial treatment fails).

Long-term treatment

(a) Prevention of new episodes

Consider long-term treatment following a single severe manic episode (i.e. diagnosis of bipolar I disorder) because, although there is no controlled evidence, the natural history of the illness implies that preventing early relapse may lead to a more benign illness course (D).

However, without active acceptance of the need for long-term treatment, adherence may be poor (II). Consider a wider package of treatment offering enhanced psychological and social support (A).

Where a patient has accepted treatment for several years and remains very well, (s)he should be strongly advised to continue indefinitely, because the risks of relapse remain high (A).

Consider extrapolating the advice concerning bipolar I to bipolar II disorder, albeit in the absence of adequate evidence from clinical trials (D).

(b) Options for long-term treatment

NB. Long-term agents are often called mood stabilizers. An ideal mood stabilizer would prevent relapse to either pole of the illness. The available medicines are probably more effective against one pole than the other (I).

At present, the preferred strategy is for continuous rather than intermittent treatment with oral medicines to prevent new mood episodes. Short-term add ons (e.g. benzodiazepines or antipsychotics) are necessary when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur or anxiety becomes prominent. Consider supplying the short-term medicines prospectively to patients to use at their discretion (D). Higher doses of the long term treatments may also be effective, instead of add ons.

Because the optimum long-term treatment strategy is not established, clinicians and patients are encouraged to participate in clinical trials designed to answer key therapeutic questions (S).

(c) Choice of long-term medicines

Consider lithium as initial monotherapy (A). Lithium monotherapy is probably effective against both manic and depressive relapse, although it is more effective in preventing mania (Ia).

Long-term treatment in general, and lithium specifically, is associated with a reduced risk of suicide in bipolar patients (I)

Consider other options if lithium is ineffective or poorly tolerated:

- Valproate probably prevents manic and depressive relapse (Ia)
- Olanzapine prevents manic more than depressive relapse (Ib)
- Carbamazepine is less effective than lithium (Ib) but may sometimes be employed as monotherapy if lithium is ineffective and especially in patients who do not show the classical pattern of episodic euphoric mania (B). Be aware of the pharmacokinetic interactions that are a particular problem for carbamazepine (A). Oxcarbazepine may be considered by extrapolation because of its lower potential for such interactions
- Lamotrigine prevents depressive more than manic relapse (Ia)

In an individual patient, if one of the above medicines led to prompt remission from the most recent depressive or manic

episode, this may be considered evidence in favour of its long-term use as monotherapy (B).

(d) If the patient fails to respond to monotherapy and continues to experience subthreshold symptoms or relapses, consider long-term combination treatment (C)

Where the burden of disease is mania, it may be logical to combine predominantly anti-manic agents (e.g. lithium, valproate, an antipsychotic) (D). Where the burden is depressive, lamotrigine or an antidepressant may be more appropriate in combination with an anti-manic long-term agent (D).

Maintenance ECT may be considered for patients who respond to ECT during an acute episode but do poorly on oral agents (D).

Consider clozapine in treatment-resistant patients (C).

(e) Rapid cycling poses particular long-term management problems

Identify and treat conditions such as hypothyroidism or substance misuse that may contribute to cycling (C).

Taper and discontinue antidepressants that may contribute to cycling (C).

For initial treatment, consider lithium, valproate or lamotrigine (A).

For many patients, combinations of medicines are required. Evaluate anti cycling effects over periods of 6 months or more by tracking mood states longitudinally. Discontinue ineffective treatments (D).

(f) Discontinuation of long-term treatment

Following discontinuation of medicines, the risk of relapse remains, even after years of sustained remission (I). Accordingly, if considered, it should be accompanied by an informed assessment of the potential costs and dangers (S).

Discontinuation of any medicine should normally be tapered over at least 2 weeks and preferably longer (A and S). Early relapse to mania is an early risk of abrupt lithium discontinuation (Ia).

Discontinuation of medicines should not be equated with withdrawal of services to patients (S).

(g) Specific psychosocial interventions

Psychosocial interventions enhance care, can increase adherence and reduce the risk of relapse (Ib).

Consider cognitive therapy specifically designed for relapse prevention for patients who suffer from frequent relapses despite the prescription of mood stabilizers (A).

Consider family therapy for patients from families with high expressed emotion (A).

User groups can provide useful support and information about bipolar disorder and its treatment (I).

Treatment in special situations

In the elderly, consider substantially lower doses of psychotropic medicines of all classes for all phases of treatment (A).

In pregnancy, there is a risk of teratogenicity from a number of the medicines used in long-term treatment (I). Lowest risks appear to be associated with antipsychotics, lamotrigine and antidepressants. Higher risks, appear to be associated with lithium < carbamazepine < valproate (A). Risks for newer compounds are not established.

In lactation, data is sparse, but none of the medicines used to treat bipolar disorder is a strict contraindication to breast feeding (D). Lithium is a relative contraindication (D). In general, a high vigilance for adverse effects on the baby should be observed (S).

Following childbirth, there is an increased risk of relapse which requires clinical awareness and effective treatment.

PART 2: CONSENSUS POINTS AND REVIEW

Fundamentals of patient management

Diagnosis

- DSM-IV criteria provide the appropriate schema for diagnosis of bipolar disorder. DSM-IV mania defines bipolar I disorder (S)
- Hypomania is not associated with significant functional impairment and, with major depression, defines bipolar II disorder (I)
- Incidence per lifetime is at least 0.5% for bipolar I disorder. Incidence per lifetime is higher for conservatively defined DSM-IV bipolar II disorder (I)
- Relapse in bipolar I and bipolar II disorder occurs with a higher frequency than in unipolar depression (I)
- Major depression is similar for unipolar and bipolar patients. Suicide is an important risk across the life span for bipolar patients (I)
- Rapid cycling is an important course specifier and may be a particular challenge for treatment (I)
- Hypomania and mania induced by antidepressants or stimulants should permit the diagnosis of bipolar disorder (IV)
- Alcoholism is the commonest significant clinical co-morbidity in Europe (I). Substance misuse is more relevant to younger patients with mania (I). Established addictive problems should be independently assessed and treated (A)
- Delay in diagnosis occurs because the illness may start non-specifically, the diagnosis of mood elevation is missed or symptoms are attributed to substance misuse or personality disturbance (II)

Key uncertainties

- Severity of mania, presence of psychotic features and the admixture of depressive symptoms may all influence outcome but are poorly characterized in relation to treatment response
- The diagnosis of hypomania in DSM-IV sets an arbitrary minimum time requirement of 4 days. Many more cases of 'unipolar' major depression appear to have had shorter periods of hypomania or simply hypomanic symptoms. The inter-relationship between hypomania, cyclothymia, borderline personality disorder, and rapid cycling sub-syndromal bipolar disorder (the bipolar spectrum) is uncertain
- The diagnosis of bipolar disorder in children is controversial. The incidence described in North America is much higher than in the rest of the world, where the illness at ages under 10 years is almost never diagnosed

Reliable diagnosis was, arguably, the major achievement of the last century in psychiatry. It depends upon the use of operational criteria to define cases, and its most important framework is

provided by DSM-IV (American Psychiatric Association, 1994). We will employ DSM-IV criteria in this text. We also recognize that in clinical practice the precise use of research criteria may be too exacting a standard. However, it is the standard to which we should aspire. Reliability of diagnosis, especially for mania, is very high under optimal conditions. The use of checklists and standardized interviews could ensure improved diagnosis under ordinary clinical conditions (Hiller *et al*., 1993).

At present, bipolar disorder is the most commonly used term to describe serial elevations of mood usually along with intercurrent depressions of mood. Descriptions consistent with bipolar disorder exist since antiquity but Kraepelin first used the term manic-depressive psychosis to include all cases of affective psychosis. Patients with unipolar, commonly psychotic depression were included in the diagnosis whether or not they had experienced mania. The central emphasis on mania and thus on bipolarity emerged relatively recently. Bipolar I disorder is defined by episodes of mania and also, usually, depression. The incidence of bipolar I disorder is estimated between 2 and 21 per 100 000 per year. The differences in reported rates are probably due primarily to the definition of cases. Differences based on first admissions to hospital, which is a proxy estimate of severity, show figures that are less variable and, on average, represent a rate of approximately 3–4 people per 100 000 per year. Incidence per life-time is approximately 0.5% for bipolar I disorder (I, Angst and Sellaro, 2000; Lloyd and Jones, 2002).

Bipolar II disorder is characterized by episodes of hypomania and, invariably, major depression. As currently defined (DSM-IV), its incidence is higher than bipolar I disorder (I, Angst, 1998).

Bipolar I disorder is prominent in secondary care because it is a highly prevalent rather than a highly incident condition. It follows a relapsing, often chronic course, with, on average, approximately eight episodes over the 10 years following diagnosis. The rate of relapse is higher than that seen in unipolar disorder of comparable severity (I, Winokur *et al*., 1993; Angst and Preisig, 1995).

The known aaetiology of bipolar disorder is primarily genetic (Ia, Potash and DePaulo, 2000). Rates of unipolar depression and bipolar disorder are elevated in first-degree relatives of bipolar patients. Compared with schizophrenia, there is weaker evidence for environmental aetiologies such as obstetric complications or inner city residence (I, Bain *et al*., 2000; Browne *et al*., 2000; Lloyd and Jones, 2002). Factors such as early abuse and neglect increase the risks for other comorbid psychiatric disorders and may worsen the course of bipolar illness (II, Leverich *et al*., 2002).

The differential diagnosis of elated states in bipolar disorder

Mania defines bipolar I disorder. DSM-IV criteria for mania, which form the basis for these guidelines, are as follows (American Psychiatric Association, 1994):

(1) A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)
(2) During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
    (a) inflated self-esteem or grandiosity
    (b) decreased need for sleep (e.g. feels rested after only 3 h of sleep)
    (c) more talkative than usual or pressure to keep talking
    (d) flight of ideas or subjective experience that thoughts are racing
    (e) distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
    (f) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
    (g) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
(3) The symptoms do not meet criteria for a Mixed Episode
(4) The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
(5) The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism)

The core symptoms of the disease must be present for 1 week and/or require hospital admission. Most critically, the criteria include a value judgement that function is impaired and one objective measure of impairment is admission to hospital. This definition of mania underpins the distinction made between bipolar I disorder and milder elated subtypes. Psychotic mania is usually regarded as reflecting severity rather than a subtype. Thus, psychotic symptoms wax and wane within individual subjects and are not invariably present from one episode to another. As a rule, psychotic symptoms in mania are mood congruent and represent an extension of grandiose interpretations, paranoid ideation or heightened awareness. They are relatively common (McElroy *et al*., 1996).

In a minority of cases, symptoms seem to be mood incongruent and in some cases this is diagnosed as schizoaffective disorder. Strictly defined schizoaffective disorder (according to DSM-IV) is relatively uncommon in clinical samples because patients must meet diagnostic criteria for both bipolar disorder and schizophrenia simultaneously. It may also be unreliable (II, Maj *et al*., 2000). The meaning of a schizoaffective diagnosis also remains controversial. It may represent forms of illness in some sense intermediate between the two Kraepelinian psychosis types, so supporting the unity of psychotic states, or it may be a categorical overlap between different disorders (II, Kendell and Gourlay, 1970; Kendell, 1987).

Although euphoric mania is the classic type of presentation, a significant number of cases of mania are far from euphoric and may have a mixture of different symptom dimensions. These dysphoric presentations require diagnostic expertise for detection and remain an area of active research. The most striking example is where patients meet the criteria for both mania and depression simultaneously, as is required for the diagnosis of a mixed state in DSM-IV. This appears to be more common in females than males. However, some significant admixture of dysphoric (depressive) symptoms occurs in many manic episodes. Recent factor analyses of the symptoms of manic patients have been relatively consistent in suggesting that the atypical features of depressive mood, irritable aggression and psychosis load on separate uncorrelated

factors (II, Cassidy *et al*., 1998; Sato *et al*., 2002). This agreement suggests the potential to distinguish several relatively separate syndromes among manic patients. Subsequent analysis has confirmed that there are at least two mixed mania presentations. One has a dominant mood of severe depression with labile periods of pressured irritable hostility and paranoia, but a complete absence of euphoria or humour. The second has a true mixture of affects with periods of classical euphoria switching frequently to moderately depressed mood with anxiety and irritability (II, Cassidy *et al*., 2001). These putative subtypes are not identified by existing diagnostic criteria and hence are not distinguished in treatment studies.

Severity of mania, presence of psychotic features and the admixture of depressive symptoms may all influence outcome but are poorly characterized in relation to treatment response. Future advice on acute treatment may take account of differential effects of medicines on the common symptom dimensions. However, at present, only severity, especially expressed as over-activity, imposes itself on current treatment options.

Although not the recommendation of DSM-IV, it is now widely accepted that antidepressant induced mania should usually be regarded as evidence of bipolar disorder (IV, opinion of the consensus group).

The diagnosis of hypomania

Both the use of the term and the criteria for hypomania remain controversial. Its definition is crucial to the diagnosis of elated states outside Bipolar I disorder. DSM-IV recognizes core symptoms of hypomania as in mania itself but with the shorter time requirement of 4 days. Patients must display observable but not impaired change in function. This will include mood elevations that are positively valuable to some individuals with bipolar disorder. In contrast ICD-10 chooses a slightly different set of symptoms and requires for hypomania, 'some interference with personal functioning'. Essentially hypomania under this definition is mild mania and should not include DSM-IV cases of hypomania. ICD-10 hypomania contributes little but confusion to current classification because it tends to encourage the use of the term for frankly manic states (IV, Goodwin, 2002). If the DSM-IV definition of hypomania is employed in prevalence studies, Bipolar II disorder remains a relatively rare condition with a rate similar to or slightly higher than Bipolar I disorder (I, Angst, 1998).

There is increasing interest in the extension of a bipolar diagnosis to a spectrum of cases with less severe elated states. This occurs dramatically if the diagnosis of hypomania is made less conservatively than in either ICD-10 or DSM-IV. When the time criterion alone is relaxed from 4 to 2 days, the numbers of cases with Bipolar II disorder inflates from 0.4% to 5.3% of the Zurich cohort. Angst makes the case for treating sub-manic mood elevation even more liberally: mood elevations or activation are identified as clinically significant if they have consequences (without specifying whether these are good or bad) (I, Angst *et al*., 2003). 'Soft hypomania' so defined expands cases with 'soft bipolar II disorder' to approximately 11% of the community sample. These reclassifications do not increase the number of patients in the population with significant mood disorder (21.3% in the Zurich population according to DSM-IV criteria), but simply redistribute approximately one-half of the DSM-IV unipolar cases to the soft bipolar II category. It follows that many treatment studies in unipolar depression using DSM-IV criteria will have included significant numbers of patients with a diagnosis of soft bipolar II disorder. These cases are often described as contributing to the 'bipolar spectrum' (Akiskal *et al*., 2000). This spectrum may also be extended to include cyclothymia, where elevation and depression of mood is subsyndromal, and temperamental 'hyperthymia'. These proposed categories do not yet have clear implications for treatment.

The differential diagnosis of depressed states in bipolar disorder

Major depression in the context of bipolar disorder is similar to major depression arising in a unipolar illness course, when severity is comparable. Within episodes of depression, grades of severity (mild moderate and severe) should be distinguished. However, bipolar patients may be more likely to demonstrate psychomotor-retarded melancholic and atypical depressive features and to have had previous episodes of psychotic depression (II, Mitchell *et al*., 2001). Retarded or psychotic depression, particularly in young people, should raise the suspicion of a bipolar illness course. However, compared with the elated states, the diagnosis of depression is relatively uncontroversial and based on criteria such as those described in DSM-IV.

Deliberate self-harm and completed suicide are important risks in bipolar disorder and are associated with depression and mixed states (I, Black *et al*., 1987; ten Have *et al*., 2002;). Assessment of risk should be as for other depression diagnoses and should follow widely accepted principles of good clinical practice (S, Hawton, 1987).

Rapid cycling

Patients with four or more episodes of depression, mania, mixed state or hypomania in the preceding 12 months are now conventionally described as showing rapid cycling. Rapid cycling thus conflates patients with frequent illnesses allowing remission between episodes with those who cycle continuously (or switch continually) from one polarity to the other without euthymia (II, Maj *et al*., 1999). The lifetime risk of rapid cycling is approximately 16% and it is weakly associated with female gender, Bipolar II disorder, current hypothyroidism and a poor response to lithium (especially the depressive component) (II–III, reviewed by Calabrese *et al*., 2001). Rapid cycling obviously implies temporal severity and it may often be difficult to treat. In 30–40% of cases, it may be preceded by exposure to antidepressants, and worsened by treatment with antidepressants (see below: treatment of depression), but there is no proof of a causal relationship.

Comorbidity

Comorbidity of bipolar disorder with a range of other psychiatric conditions poses problems of diametrically different kinds. First, non-specific psychological symptoms and disturbed behaviour may be the harbinger of bipolar disorder in young people. Diagnostic uncertainty or the wrong diagnosis at the very early stages of the illness can delay its accurate recognition (I, Lish *et al*., 1994). Second, in the presence of recognized bipolar disorder, comorbid conditions may contribute to poor treatment response and outcome. Community samples show high lifetime comorbidities of Bipolar I disorder with a range of other anxiety related disorders and substance misuse (I, Kessler *et al*., 1997). Lifetime rates are

extremely high: as many as 93% of patients may at some time have had an anxiety disorder (I–II, reviewed by Freeman *et al*., 2002). This raises the question of whether anxiety symptoms are best viewed as part of the behavioural phenotype in bipolar disorder, if only at some stage in its development. The earliest symptoms that a patient experiences may be those of anxiety but the dominant picture subsequently may be mania and depression. On the other hand, anxiety is not uncommon between acute episodes and in bipolar depression. Where the anxiety disorder dominates the outcome, this must clearly influence evaluations of successful treatments.

The risk of alcohol dependency is another common and clinically significant comorbidity of Bipolar I and II disorder. Drug misuse, especially stimulant misuse, is more relevant to younger patients with mania and is associated with poorer outcome. It can confound the diagnosis and makes engagement with treatment more difficult (I, Strakowski *et al*., 2000). Indeed, mania appears to be induced by a range of stimulant drugs. Where elated states are sustained and meet criteria for mania, a diagnosis of 'drug-induced psychosis' is likely to be wrong and a diagnosis of bipolar disorder more useful. A true drug-induced psychosis should either wane with the clearance of the offending drug or be a transient effect associated with drug withdrawal (see definition of Substance-induced psychotic disorder in DSM-IV).

L-Dopa and corticosteroids are the most common prescribed medications associated with secondary mania (I–II, Young *et al*., 1997; Brown *et al*., 1999, 2002).

It is an important principle that bipolar patients with significant substance or alcohol misuse should have these issues appropriately assessed and treated, and consideration given to involving the specialist drug and alcohol team, or dual diagnosis team, if available. There is evidence that effective treatment of substance misuse can improve compliance and bipolar outcomes (Ib, Salloum and Thase, 2000).

Personality disorder may be an important Axis II accompaniment of bipolar disorder, although the categorical approach to personality disturbance has important limitations (II, Blacker and Tsuang, 1992). As with the comorbidities already described, the greater risk lies in allowing a personality diagnosis to blind the clinician to bipolar disorder, rather than vice versa. The relationship between borderline symptoms, bipolar spectrum and rapid cycling bipolar disorder remains most uncertain.

Organic conditions, such as thyroid disease, multiple sclerosis or any lesion(s) involving right-sided subcortical or cortical areas may be associated with secondary mania (II–III, Cummings and Mendez, 1984; Strakowski *et al*., 1994; Mendez, 2000) and should be considered in the differential diagnosis.

Early diagnosis of bipolar disorder

The early diagnosis of bipolar disorder may not be easy. The delay described in surveys of patients with bipolar disorder is, on average, a decade (I, Lish *et al*., 1994). A number of factors contribute. In part, and as noticed in the previous section, it will be because the first developments may be non-specific anxiety or depressive symptoms of relatively minor severity, or substance misuse. Bipolar disorder cannot be diagnosed if mood elevation is not manifest, and it is unhelpful to say that a diagnosis has been missed in these circumstances. There is particular uncertainty surrounding the diagnosis of bipolar disorder in children. The problem is beyond the scope of this review and is highly controversial because major differences exist in practice between North America, where childhood and adolescent diagnoses appear to be common (II, Geller *et al*., 1995), and the rest of the world, where they are not (II, Wals *et al*., 2001). Prospective studies to validate the childhood diagnoses are ongoing. However, affective instability in childhood is described retrospectively by patients and often conceptualized as part of the illness whether this is scientifically justified or not.

Notwithstanding the reservations of the previous paragraph, the diagnosis of (hypo)mania or subsyndromal mood elevation may indeed be missed in young adults. Misdiagnosis contributes to the problems for patients and their families when accepted diagnostic criteria are either not applied or ignored. In young patients, generally, behavioural disturbance may be interpreted as the maturational tensions of adolescence. Alternatively, 'personality' diagnoses are still perhaps too readily employed (III, Tyrer and Brittlebank, 1993). To miss a diagnosis of a treatable condition may be harmful, whereas to miss a diagnosis of personality disorder may be inconsequential. Second opinions from bipolar specialists are potentially helpful.

Finally, before the expression of frank (hypo)mania, a significant number of bipolar patients diagnosed with unipolar depression may run into difficulties because of inadequate or inappropriate treatment. Any patient who is being treated for depression should be asked if they have a personal history of abnormal mood elevation of any duration or a family history of affective disorder (opinion of consensus group).

Access to services and the safety of the patient and others

- Assessment should be offered by a trained psychiatrist with an understanding of both the medicines and psychological treatments available for the management of bipolar disorder (S)
- Patients should have access to early intervention, which must include the option of hospital admission (S)
- Appropriate use of legal powers of detention is essential for the successful management of risk in some patients with acute mania and severe depression (S)
- Consistent outpatient follow-up is necessary and many individual patients may require complex interventions in community settings (S)
- The omission of specific recommendations for bipolar patients from Department of Health plans in the UK implies a current lack of understanding among policymakers of the need for high quality specialized services for bipolar patients (IV). The burden of disease for bipolar I disorder is comparable with schizophrenia (I)

Any acute episode, regardless of polarity, should receive active treatment. Mania, in particular, is a relative emergency because of the important personal and social consequences that result from the errors of judgement that are intrinsic to a highly elevated mood state. The complexity of bipolar disorder makes it desirable that assessment should be offered by a trained psychiatrist with an understanding of both the medicines and psychological treatments available for the management of bipolar disorder. Patients should have access to early intervention, which must include the option of hospital admission. Appropriate use of legal powers of detention is essential for the successful management of some patients with

acute mania and psychotic depression. Patients who are unlikely to cooperate with treatment because of difficulties in accepting their diagnosis, who misuse drugs, or in whom violence, risk taking or self-harm complicate their mood change may require complex, community-based interventions, although the optimal approach remains controversial (II, Burns *et al*., 2002).

Suicide is an important risk for patients with bipolar disorder, primarily when depressed or in a mixed state where depressive symptoms are prominent (I, Harris and Barraclough, 1997).

The apparent neglect of the specific needs of bipolar patients in UK government policy (IV, Morriss *et al*., 2002) suggests we may not be stating the obvious in the previous paragraphs. The term bipolar disorder or manic depression was given no special consideration (and entirely omitted from the glossary of key terms) in the National Service Framework for mental disorders in the UK (Department of Health, 1999).

The relative neglect of bipolar I disorder in comparison with schizophrenia is seen on a variety of indicators of research activity, despite a comparable burden of disease (Ia, Clement *et al*., 2003).

Very little work has pragmatically addressed the best model of service delivery for bipolar patients. To take the issue *a priori*, there is a need for informed polypharmacy and accurate assessment of the mental state. This means that a trained psychiatrist should always be directly involved in patient management.

Enhanced clinical care

- Enhancement of patient care can be achieved by structured interventions based on principles derived from behavioural and cognitive psychology (Ib). This has the potential to complement and inform treatment with medicines, not replace it (IV)
- Although the best evidence for efficacy comes from adding psychological treatments to routine care, the objective should be to enhance routine care itself (S)

Key uncertainty

- The optimal approaches to enhanced care have not been empirically established

Good clinical practice is a commonplace but worthwhile objective, which we do not underestimate. Doctors must take responsibility for diagnosis, physical examination, investigations and explanation of the medical plan of management. They must communicate clearly and effectively. A therapeutic alliance between doctor and patient is essential for the management of any complex chronic condition, which bipolar disorder certainly is.

The role of structured psychological treatment in the management of bipolar disorder remains at an experimental and exploratory level. However, the findings are already important because they show formally that enhanced care can improve outcomes in Bipolar I patients. Broadly speaking, the interventions that have been offered in bipolar disorder are pragmatically directed to identified clinical problems. They do not depend on specific models of psychopathology. There may also be appreciable overlap in content of the different approaches although it will be convenient to consider them under separate headings.

Knowledge (or 'psycho-education')

Doctors, patients and carers tend to bring different experiences and beliefs to the therapeutic relationship (II, Lingam and Scott, 2002). It is not surprising that they make different estimates of future risks. There is a consensus that good clinical management of patients with bipolar disorder involves an appreciable educational component for both patients and their relatives. Successful long-term management involves a high degree of patient involvement and autonomous judgement about return of symptoms, etc. It is essential to address the seriousness of the illness, any reluctance to give up the experience of hypomania or mania, the risk of relapse and the benefit of therapeutic engagement (D). For patients to know what to do, and why, appears usually to be an essential prelude to actually doing it.

One option is to provide a group course, the efficacy of which was recently shown in a RCT (Ib, Colom *et al*., 1998; Colom *et al*., 2003). Current practice also favours didactic teaching, live or by video, written materials or guided internet searching for high quality material (e.g. the National Electronic library for mental health: http://www.nelh.nhs.uk/). Early in the illness course may not be the most propitious for patient acceptability, so the goals of education need to be sustained and incremental. There also needs to be a shared and consistent approach across mental health disciplines.

Adherence to medicines

As we will show, there is good evidence that long-term treatment is effective in preventing relapse in bipolar disorder. However, adherence to prescribed medicines is poor in most chronic illness (I, Horne and Weinman, 1999). Bipolar disorder is no exception (I and II, Johnson and McFarland, 1996; Lingam and Scott, 2002; Scott and Pope, 2002). Side-effects are a major consideration given the limitations of existing medicines and should be minimized by all possible means. These include dose adjustments, once daily administration (e.g. at bed time) and switching between formulations. Other efforts to improve compliance such as user-friendly packaging, monitoring of pill taking, and even delivery of supplies of medicine may contribute to successful treatment in certain individuals.

However, the motivation to take tablets is also heavily dependent upon the attitudes, beliefs and perceptions of risk shown by patients and their carers. These cultural factors may often divide clinical staff from patients. Approaches to improving adherence can be based on a systematic theory of self-regulation (Leventhal *et al*., 1992). This should allow quite specific interventions to be developed in the future.

A brief six-session cognitive therapy package compared to usual outpatient follow-up led to significant improvements in adherence with lithium and reduced admissions, but this study is only now being replicated (Ib, Cochran, 1984; Scott and Tacchi, 2002). Pragmatic motivational interviewing to improve adherence to prescribed medicines has also been shown to be moderately effective in patients with psychosis. The best-known study included a subgroup with bipolar disorder (Ib, Kemp *et al*., 1998). Because non-adherence with treatment occurs in up to 50% of most clinical samples, the development of a focused and generally applicable approach to this problem would be welcome. The published methodology emphasizes the involvement of a third party and there is clearly a potential role here for pharmacists who occupy an advisory role for patients in other contexts.

A recurring theme in this document will be the paucity of evidence on some key issues for treatment. Clinical trials, in bipolar disorder as in other conditions, are likely directly to enhance patient care (Ia, reviewed by Ashcroft, 2000). We believe that participation *per se* in well-designed clinical trials is a benefit

for both doctors and patients. To put it bluntly, a controlled experiment is likely to be better than participation in the uncontrolled experiment that is ordinary practice. Furthermore, the results from trials will eventually enhance the evidence base for improving patient care.

Awareness of stressors, sleep disturbance and early signs of relapse, and regular patterns of activity

Manic relapse in particular may follow a relatively stereotyped course in individual patients. Sleep disturbance is perhaps the most commonly described final common pathway to mania, although other impulses and preoccupations may accompany it or precede it (II, Wehr *et al*., 1987). Efforts to train patients on individual scripts which access their own experience and enable them to take evasive action appears to be effective in avoiding new episodes of mania (Ib, Perry *et al*., 1999). Interestingly this approach was less successful with episodes of depression. This was a single intensive trial involving up to 12 sessions of training and there is again a need to know how its impact can be made more widely applicable. The involvement of family members is often helpful but must be treated sensitively as it may not always be welcome.

Interpersonal social rhythms therapy (IPSRT) developed out of particular ideas about what behavioural features contribute to relapse in bipolar disorder (II, Swartz and Frank, 2001). It was strongly influenced by the idea that bipolar disorder is characterized, at least in part, by disturbed biological rhythms that may arise as a consequence of disruptions in social routine. The reestablishment of regular habits for those behaviours that occur at least once per week is a primary goal in treatment. Although IPSRT appears to reduce the time to recovery of bipolar depressive episodes compared to intensive clinical management (Ib, Frank *et al*., 1994), IPSRT has not proved effective in relapse prevention.

The further role of structured psychotherapy will be considered in more detail below. All such therapy recognizes as axiomatic the value of a highly collaborative therapeutic relationship with the patient. The commitment by a clinician to see a patient long-term can contribute to an optimal management plan.

The general point emerges that outcomes for patients can be improved without either a new medicine or combination of medicines. Translating this observation into enhanced care for more patients should be an important objective for treatment.

Functional impairments

Clinicians must anticipate the need to give advice about expectations and capacity to work. Major life decisions may not be auspicious when made in a depressive or manic state. Furthermore, patients may experience considerable difficulty performing at the level for which their education may have prepared them (II, review by MacQueen *et al*., 2001). This may be a result of common subsyndromal symptoms of depression or anxiety (I, Denicoff *et al*., 2000) or other barriers to psychological well being (II, reviewed by Scott, 1996). Factors specific to bipolar disorder, such as experience when high or personality style, may also conspire to widen the gap between aspiration and achievement. Finally, there is evidence that objective impairments of neuropsychological function are both significant and enduring (II, Clark *et al*., 2002; Rubinsztein *et al*., 2000).

The National Service Framework for Mental Health recognized the vital role of informal carers in the delivery of mental health care (Department of Health, 1999). However, it treated the needs of adults of working age as generic and was probably influenced by evidence from research in schizophrenia (I, Fadden *et al*., 1987) and the dementias (I, Clyburn *et al*., 2000). The literature concerning bipolar disorder is sparse, but the perceptions and beliefs of carers about it, as for other diseases, may have important effects on levels of burden that are experienced (II, Perlick *et al*., 1999). There is scope to develop improved psychosocial interventions tailored to bipolar patients and their families. A particular uncertainty, neglected hitherto, is the impact of manic states upon carers, and indeed their children.

Treatment of different phases of bipolar disorder

Terminology and treatment strategy

- Bipolar disorder usually presents for treatment in an acute illness episode (mania, depression or mixed state) (I). The objective of short-term treatment is to reduce the severity and shorten the duration of the acute episode (S)
- Long-term treatment is indefinite for the prevention of new episodes and to achieve adequate inter-episode control of residual or chronic mood symptom (S)
- Because of the high risk of relapse and the apparent progression to more frequent episodes, long-term treatment with appropriate medicines is advocated from as early in the illness course as is acceptable to a patient and their family (D)
- Between episodes, mood instability or chronic depressive symptoms are common (I) and generally underestimated

Key uncertainty

- Current strategies emphasize the treatment and prevention of syndromal relapse. Disabling aspects of long-term outcome such as chronic depressive symptoms or enduring neurocognitive impairment may be important future therapeutic targets

For the most part, bipolar disorder runs an episodic course. It is usual therefore to think of it as a sequence of acute illness episodes (mania, depression or mixed states) interspersed by relative euthymia. This view of the illness conditions how treatment strategies and actual treatment phases are distinguished. Short-term treatments will refer to episodes and will imply the intention to discontinue a medicine on recovery. Long-term treatment is indefinite and for the prevention of new episodes. Although it is conventional in discussing unipolar disorder to distinguish relapse (the return of symptoms treated in an acute episode) from recurrence (the return of new symptoms), this is a distinction that is sometimes not helpful in bipolar disorder with frequent episodes. We will refer to long-term treatment for prevention of relapse.

Chronic symptoms in bipolar disorder are commonly depressive (II, Judd *et al*., 2002). As already noticed, there are also cognitive distortions similar to those seen in depressive disorder (II, Scott, 1996) and neuropsychological deficits that are still largely ignored (II, Rubinsztein *et al*., 2000; Clark *et al*., 2002). These disabling aspects of long-term outcome are often either neglected or accepted as the natural history of the disease. As potential measures of clinical outcome, along with measures of social adjustment, they represent key areas of current uncertainty.

Acute manic or mixed episodes

- Antipsychotics, lithium and valproate all have anti-manic actions (Ia or Ib)

- Treatment choice should be dictated by the clinical context and, whenever possible, by patient preference and experience (S)
- Typical antipsychotics have been widely and appropriately used for the treatment of highly active and/or agitated patients with mania (Ib). Doses producing extrapyramidal side-effects (EPS) should only be tolerated for the shortest necessary period of time and, if possible, avoided. Anti-cholinergic agents can reduce the burden of EPS (Ib)
- The atypical antipsychotics (olanzapine, ziprazidone, aripiprazole, quetiapine and risperidone) have shown efficacy in monotherapy placebo controlled trials in mania (1b)
- Atypical antipsychotics are less likely to produce EPS (1a), which is of particular significance in bipolar disorder because of an apparently greater risk of motor side-effects, including tardive dyskinesia (IIa)
- Combination of an antipsychotic with another anti-manic agent appears to facilitate the acute treatment response, especially when patients show breakthrough mania with the first agent. Risperidone, haloperidol, olanzapine and quetiapine, when combined with lithium or valproate, have been shown to be superior to lithium or valproate alone (Ib)
- Benzodiazepines are useful adjunctive agents and can induce sedation or sleep (Ib)
- Discontinuation of short-term treatments for mania can be considered after full remission of symptoms. The required duration will often be of the order of 12 weeks, although higher doses of antipsychotics may be reduced earlier (IV)

Key uncertainty

- Switch to depression after mania may occur in any illness course: it is not established which treatments, if any, make this more likely

Antipsychotics

Mania can develop extremely quickly and give rise to risks both for the patient and for others. In its more severe form, mania is almost invariably treated with antipsychotics and patients with psychotic mania were among the first patients treated successfully with chlorpromazine. The older, so-called typical, antipsychotics have been the mainstay of treatment in all countries where practice has been systematically audited (II, reviewed by Cookson, 2001). They are anti-manic not simply sedative. However, placebo-controlled data to show that any older antipsychotic works in mania is very limited (Ib, Johnstone *et al*., 1988). Clinically, we depend heavily upon the evident short-term effect of tranquillization, observable in clinical practice and under trial conditions (Ib, van Leeuwen *et al*., 1977), but perhaps too often produced with excessively high doses. There is little good evidence to guide the choice of dose, but, for example, increasing the dose of haloperidol above 30 mg per day is not justified.

The availability of parenteral preparations is valuable in emergency situations and should form part of any local protocol for treating highly agitated patients (Ia, Allen *et al*., 2001). Previously, often in an effort to achieve sedation, patients were habitually treated with high doses of, for example, haloperidol or droperidol (the latter now withdrawn in the UK), which produced marked extrapyramidal symptoms unless combined with an anticholinergic agent. Where possible, EPS should be avoided, even in a crisis.

If sedation is the aim, then benzodiazepines such as diazepam, lorazepam and clonazepam are more appropriate and can usually produce adequate sedation. When prescribed regularly at night, they may also facilitate return of a normal sleep wake cycle (II, reviewed by Post *et al*., 1996).

There is a pivotal comparison of chlorpromazine with lithium (Ib, Prien *et al*., 1972). This showed, albeit in a secondary analysis, that the most active patients were more satisfactorily treated with chlorpromazine than with lithium. Pragmatic measures of efficacy (patient drop-out and reduction in nursing demands) were particularly convincing for clinical practice. The use of chlorpromazine, haloperidol and, by extension, other similar antipsychotics with an essentially analogous action is justified by this and other studies (Ib–III, reviewed by Cookson, 2001). However, clinicians should be mindful of the limits of the available evidence.

The primary mode of antipsychotic action is still probably dopamine blockade, although there is controversy about the precise mechanism at receptor level (Kapur and Remington, 2001). While the neurobiology of mania is also poorly understood, mania may be a hyperdopaminergic state appropriately treated by blockade of dopamine receptors. Accordingly, RCTs have now been completed showing the efficacy of atypical antipsychotics as monotherapy compared with placebo in mania. These include olanzapine (Ib, Tohen *et al*., 1999, 2000), ziprazidone (Ib, Pfizer, outline presentation), aripiprazole (Ib, BMS, outline presentation), quetiapine (Ib, Astrazeneca, outline presentation) and risperidone (Ib, Johnson and Johnson, outline presentation). Olanzapine and ziprasidone exist in parenteral form for acute use, risperidone is available in a long acting injectable formulation.

Currently, olanzapine is the only agent licensed for acute mania in the UK (as Zyprexa®). Risperidone has a license for ‘psychosis’ (as Risperdal®).

As in schizophrenia, the argument between the merits of typical versus atypical antipsychotics is less about efficacy than about side-effects. Atypical antipsychotics have a lower risk of EPS than the older antipsychotics (especially when used at higher doses), in acute schizophrenia (Ia, Geddes *et al*., 2000). Bipolar patients are probably more likely than patients with schizophrenia to show acute EPS when treated with comparable doses of haloperidol. While this has long been suggested, comparative data from pooled studies conducted with identical methodology appear to prove it (outline presentation, Lilly). Naturalistic studies in schizophrenia suggest that acute EPS are predictive of subsequent tardive dyskinesia (reviewed by Andrew, 1994).

The trials with atypical antipsychotics show that an anti-manic action can be achieved without EPS (Ib, reviewed by Keck *et al*., 2000). This is an important clinical message, which should influence prescribing practice, for all antipsychotics. As in schizophrenia, atypical antipsychotics may be increasingly preferred to typical antipsychotics because of their superior therapeutic ratio.

The use of lithium and valproate, and not antipsychotics, as first-line treatment for mania has been emphasized in the USA. Initially (Frances *et al*., 1998), this was to the exclusion of antipsychotics, which were reserved for adjunctive treatment (primarily of psychotic symptoms and agitation) and for sedation. Whatever the expert preference for lithium or valproate, it was clear from a number of systematic audits that the US guideline conflicted with actual clinical practice, where the great majority of

patients with mania were treated with antipsychotics (II, Chou *et al*., 1996), often as monotherapy. European practice, and perhaps that of the rest of the world, has always favoured antipsychotics as first-line agents, partly perhaps because of a greater emphasis on more severely disturbed patients (reviewed by Licht, 1998).

The emergence of data supporting the use of olanzapine for mania has resulted in its inclusion in revised APA guidelines. Lithium, valproate and the antipsychotic, olanzapine are now the first-line recommended treatments for mania (APA, 2002). While olanzapine has the best-published data to this point, the satisfactory use of classical agents and the emerging evidence for other atypicals, justify a broader acceptance of antipsychotics in these guidelines, although further independent trials to guide clinical practice would be welcome.

Other anti-manic medicines: lithium, valproate and carbamazepine

In severe or highly active states, lithium appeared to be less effective than chlorpromazine (Ib, Prien *et al*., 1972).

Valproate is the generic term often used to describe different formulations of valproic acid, the active chemical entity. Sodium valproate has been widely used in epilepsy and is also available in a sustained release preparation. Valproate semisodium (also known as divalproex) is a non-covalent dimer molecule and has been produced in several formulations, including a slow release form. In bipolar disorder, valproate has been studied almost exclusively as valproate semisodium and is licensed in the UK as Depakote®. (For information on dosing of different formulations, see Appendix.)

Valproate semisodium has been shown to be effective in severe mania (Ia, Macritchie *et al*., 2003), when the dose should be titrated upwards quickly to obtain control: 750 mg on day 1 and 20 mg/kg on day 2. Previous US Guidelines gave unusual weight to the efficacy data for valproate and the conviction that lithium and valproate are 'mood stabilizers' (see below).

The use of lithium, valproate or an antipsychotic as monotherapy is appropriate for the treatment of less severe manic states. Lithium or valproate may also be preferred, or instituted together with an antipsychotic, when it is planned to continue them for long-term treatment (see below).

Carbamazepine has anti-manic efficacy (Ib, reviewed by Okuma and Kishimoto, 1998) but is rarely advocated for first line treatment.

The combination of an antipsychotic with lithium or valproate in acute mania

In practice, patients may already be taking lithium or valproate when mania occurs as a breakthrough during long-term treatment. Under these conditions, it would be common to optimize the maintenance treatment and add an antipsychotic agent. Evidence is available for risperidone, haloperidol, olanzapine and quetiapine that, when combined with lithium or valproate, the combination may, indeed, be superior to monotherapy with lithium or valproate in acute mania.

In an episode of mania occurring in a patient not on long-term treatment, the APA guidelines advocate combination of lithium or valproate with an antipsychotic de novo. This is in preference to antipsychotic monotherapy. This may be rational when there is a wish to spare the antipsychotic dose (Ib, Muller-Oerlinghausen *et al*., 2000) or long-term treatment with lithium or valproate is planned. However, the combination may not be more efficacious than monotherapy when started together. The combination effect is best seen in patients who are either partial responders or have broken through on monotherapy (Ib, Sachs *et al*., 2002).

Carbamazepine is not the optimal partner for combination therapy because its liver enzyme inducing properties may reduce the levels of other agents, which, in turn, may inhibit the catabolism of carbamazepine (Ia, Monaco and Cicolin, 1999).

Benzodiazepines: Benzodiazepines such as diazepam, lorazepam and clonazepam are useful in the management of acutely agitated manic states (Allen *et al*., 2001). They are adjunctive, in the words of North American guidelines. They are indicated when sedation or tranquillization is a priority and when there is a pressing need to induce sleep. Their safety in relatively high sedative doses and the absence of important pharmacokinetic interactions with other agents are advantages.

The use of adjunctive benzodiazepines can help to avoid excessive doses of antipsychotics with the attendant risk of cardiovascular and other side-effects, including neuroleptic malignant syndrome.

Antidepressants and mania: As noticed previously, mania may develop in patients taking an antidepressant. The antidepressant may have contributed to the manic episode and should be tapered and discontinued. The duration of such episodes tends to be shorter and the symptoms less severe.

Contrast with North American recommendations for treatment of mania

These recommendations are different from North American guidelines on two main issues:

- Antipsychotics as effective first line anti-manic agents
- The lack of emphasis on long-term treatments ('mood stabilizers') in acute phase treatment of mania

We accept that the quality of the existing data is limited. However, the short-term efficacy of typical antipsychotics is a clinical reality, and their parenteral use is a frequent necessity in highly active and aggressive patients. It makes little sense to deny their place in clinical management on the grounds that they have not been shown superior to placebo in less disturbed patients entered into controlled trials with very high drop-out rates.

The issue of long-term treatment with lithium and valproate will be addressed below. While it may often make sense to use one or both agents in acute mania in combination with an antipsychotic, there are no particular reasons for making this mandatory. In particular, lithium is sometimes difficult to use in exhausted, dehydrated patients. Where mania can be treated with a monotherapy in its early stages, this appears to be preferable to automatic prescription of a combination. As explained above, the effect of combination is most striking when patients have developed mania as a breakthrough while taking lithium or valproate, not where a combination is started *de novo*.

Finally, efforts to prescribe lithium to patients who are poorly compliant with it may be misplaced. Lithium discontinuation by patients is extremely common and is associated with admission to hospital (I, Johnson and McFarland, 1996). This association will be due, in large part, to manic relapse, which is provoked by abrupt lithium discontinuation. Unless patients are adherent to lithium for

a minimum of 2 years, these withdrawal effects will nullify any potential prophylactic effect (Goodwin, 1994).

The switch into depression following mania

It is often stated that treatment with typical antipsychotics is more likely to result in patients switching from mania into depression than treatment with lithium or valproate. This is also a reason that is sometimes given for preferring atypical to typical antipsychotics. Evidence in this area is very limited and all conclusions are confounded by the natural history of the illness. Recent data from the lamotrigine/lithium/placebo trials suggest that the risk of relapse of the index episode was higher than the risk of switching (outline presentation, GSK).

Where olanzapine has been compared with haloperidol, the difference in switch rates to depression was not impressive (Ib, outline presentation, Lilly). Comparable data for other atypical antipsychotics will be of interest. At present, it would be unwise to base an acute treatment strategy on the assumed risk of switch to depression. However, high doses of antipsychotics may cause akathisia and be dysphoriant in their own right and this should be avoided.

Short-term treatments for mania, particularly benzodiazepines and antipsychotics, should be reduced in dose as the manic state improves: lithium and valproate should be reduced only after complete remission of symptoms and preferably after 8 or more weeks of euthymia. Lithium discontinuation over at least 2 weeks is advised. Tapering may also be preferable to sudden discontinuation for valproate (consensus opinions).

Short-term treatments of mixed states

The strict diagnosis of a mixed state requires criteria for a manic episode and a major depressive episode to be met simultaneously for 1 week. Most treatment recommendations have resulted from subgroup analysis of data from mania trials. In a reanalysis of the data from the valproate/lithium/placebo acute treatment trial (Ib, Bowden *et al*., 1994), cases with 'psychotic' and 'classic' mania showed equal valproate and lithium response rates (Ib, Swann *et al*., 2002). Only irritable dysphoric (rather than depressed) cases showed an advantage to valproate over lithium. Caution is required when such post-hoc analysis generates a conclusion at variance with the main effect seen in the trial (lithium and valproate were equal), as it may have arisen by chance and will then be misleading. A proportion of patients entering the study were already known to be non-responders to lithium, which may also have influenced the results.

A secondary analysis of strictly defined mixed states to compare combination treatment with olanzapine or placebo as cotherapy with valproate or lithium suggested that mixed cases had a slightly higher rate of response to the olanzapine addition (Ib, Tohen *et al*., 2002).

There is no indication either to start or continue treatment with an antidepressant in a mixed state. However, the status of predominantly depressed mixed states or agitated depression is uncertain and pragmatic treatment may require an antidepressant in combination with an antipsychotic, lithium or valproate.

ECT

ECT may be considered for manic patients who are severely ill and/or whose mania is treatment-resistant, those patients who express a preference for ECT and patients with severe mania during pregnancy (C). Evidence for efficacy in mania is limited, in part because patients with severe mania are difficult to enter into trials. However, audit findings support efficacy (Mukherjee *et al*., 1994).

It is more usual for ECT to be considered in depression (see below).

Short-term treatment of depressive episodes

- Antidepressants are effective for treating depression in bipolar disorder (Ia)
- Severe depression in a bipolar I illness course should be treated with an effective antidepressant in the presence of another agent that will reduce the risk of mania (lithium, valproate or possibly an antipsychotic) (A)
- The risk of a switch to mania is greater for tricyclic antidepressants compared with other antidepressants (SSRIs in particular, Ia)
- While unlikely to provoke a manic switch, lithium, valproate and carbamazepine have inadequate evidence for acute antidepressant efficacy
- Lamotrigine has limited evidence for acute efficacy (Ib)
- Discontinuation of an antidepressant should follow BAP recommendations for unipolar depression but with a more rapid taper out in rapid cycling patients (D)

Key uncertainties

- There is a paucity of evidence to decide between different agents in the treatment of bipolar depression
- Refractory depression is not uncommonly associated with a bipolar illness course. There is no specific recommendation for bipolar patients, and treatment should follow recommendations for refractory depression in general
- It is uncertain whether the treatment of bipolar spectrum disorder cases with depression should be different from the treatment of unipolar cases

If we were to reflect the relative burden of disease, this guideline would be largely about treating depression. However, it would also be remarkably short. There is a paucity of placebo-controlled efficacy data for major depression arising in the course of bipolar disorder.

Antidepressants

Meta-analysis suggests that conventional antidepressants (imipramine, fluoxetine and tranylcypromine) are, on average, superior to placebo in the acute treatment of bipolar depression (Ia, Gijsman *et al*., 2003). However, the number of studies and the numbers of patients in the studies are low. By contrast, there has been a very large number of trials examining the efficacy of many different antidepressants in unipolar major depression (Ia, Anderson, 2001; Storosum *et al*., 2001). These studies systematically excluded patients with a Bipolar I course. Accordingly, it would be unwise to extrapolate specific findings from the unipolar literature to the treatment of bipolar disorder. However, the general finding of antidepressant efficacy may apply to bipolar depression.

The response to the same treatments in hospitalised unipolar and bipolar patients has been audited carefully in the Munich case series (II, Bottlender *et al*., 2001; Moller *et al*., 2001): the severity of illness and times to response with tricyclic antidepressants

appear identical. The most important difference relates to the switch to mania and this will be addressed below.

The anergic pattern of illness often seen in bipolar patients favours the use of activating antidepressants such as monoamine oxidase inhibitors, including moclobemide.

The virtual absence of data specifically for bipolar depression contrasts with the vast literature for unipolar depression and the widespread use of antidepressants to treat bipolar depression. It creates a major paradox for treatment recommendation in this area. In the USA, the favoured approach has been to concentrate exclusively on the very small literature addressed specifically to bipolar depression and to produce essentially qualitative conclusions (e.g. Compton and Nemeroff, 2000). The recommendation that has resulted is for the use of lithium or bupropion as first line treatment for depression in bipolar illness (American Psychiatric Association, 2002). This is not a recommendation that can be uncritically accepted.

ECT

ECT is also effective in severe depression: the relevant trials will have included bipolar cases, although trials exclusively in bipolar disorder do not exist (Ia, The UK ECT Review Group, 2003). Beliefs about ECT in the general population appear to remain influenced by unfavourable media portrayal (Lebensohn, 1999). While clinicians have a responsibility not to pander to ignorance and prejudice, it may be helpful to allay fears that ECT is often used against the will of individual patients (S).

It is unusual for ECT to be used against a patient's will, even in services with a high utilization rate: outcomes appear reassuring (Wheeldon *et al*., 1999).

Lithium in depression

Treatment guidelines (Sachs *et al*., 2000) repeatedly suggest an overwhelming expert preference for the use of lithium as first-line treatment rather than antidepressants. However, the actual evidence for acute efficacy of lithium in bipolar depression, either as a sole agent or in combination with others, is disappointing (Ia, Bhagwagar and Goodwin, 2002). Even in maintenance treatment, its efficacy specifically against depression is being questioned (see below). Nevertheless, it remains a key comparator for new studies in bipolar disorder.

Anticonvulsants in depression

Carbamazepine and valproate have an inadequate evidence base in acute depression, despite recommendations to use them. Lamotrigine has one published study, which suggested benefits in bipolar depression compared with placebo (Ib, Calabrese *et al*., 1999) and a second study was also supportive (IIa, Frye *et al*., 2000).

Antipsychotics in depression

There is currently no indication to use antipsychotic agents to treat bipolar depression as monotherapy. However, preliminary data from a large RCT show that olanzapine has a modest antidepressant effect in bipolar I depression compared with placebo (Lilly, outline presentation). Antipsychotics have a place in the management of psychotic depression (Ib, Johnstone *et al*., 1988).

The risk of a switch to mania during treatment of a depressive episode

One short-term outcome of treatment for depression is a switch to mania. This may occur as a consequence of illness course or because some treatments have a greater potential to cause switching than others. In a meta-analysis of patients without a previous history of mania, treatment with tricyclic antidepressants was twice as likely to result in a manic event as treatment with SSRIs or placebo (Peet, 1994). In short-term bipolar treatment trials with antidepressants, switch rates were low but there was again a higher rate of switch for tricyclic antidepressants compared with other antidepressants (SSRIs in particular) (Gijsman *et al*., 2003).

The Munich audit data, and clinical common sense, suggest that an anti-manic in combination with the antidepressant may reduce the risk of a manic switch in depressed patients with a high risk of mania. The anti-manic agent could be valproate, lithium or an antipsychotic. Preliminary reports of a large placebo-controlled trial in bipolar patients suggest that fluoxetine plus olanzapine is effective in reducing depressive symptoms without provoking manic relapse (Lilly, outline presentation). Again, this appears to support the general recommendation to combine an effective antidepressant with an anti-manic agent.

Discontinuation of short-term treatment for depression

There is uncertainty about the value of long-term treatment with antidepressants, so it is frequently implied that early discontinuation is desirable (Montgomery *et al*., 2000).

Both the anti-manic and the antidepressant medicines should be terminated together if the intention is that treatment should be simply for an acute episode. Discontinuation of an antidepressant should follow recommendations in related BAP guidelines and taper over 4 weeks if possible (Anderson, Nutt *et al*., 2000). In particular, the possibility of adverse withdrawal effects should be discussed and reassurance offered.

Paradoxical manic episodes have been described during withdrawal of antidepressants (Goldstein *et al*., 1999).

In patients who do switch to mania during treatment, the antidepressant should be tapered and discontinued (consensus opinion).

Long-term treatment

- The term 'mood stabilizer' should be used more carefully. It could be reserved for agents that have been shown to prevent relapse to either pole of the illness about equally (D). It seems more likely to be used more liberally for agents active against one pole of the illness and shown not to make relapse to the other pole more likely. Neutral reference to long-term treatment will be preferred here
- Lithium prevents relapse of mania but is relatively less effective against depression (Ia). The highest dose that produces minimal side-effects should be employed. Levels below 0.5 mmol/l are usually too low. Lithium may be effective in a minority of patients as monotherapy (I)
- Lithium probably reduces the risk of suicide (II)
- Valproate may be as effective as lithium in the prevention of relapse (Ib)
- Carbamazepine as monotherapy is less effective than lithium (Ib)
- Olanzapine also prevents relapse of mania but is relatively less effective against depression in long-term use (Ib)
- Lamotrigine is more effective against depression than mania in long-term treatment (Ib) and should be considered where depression is the major burden of the illness (A)

- Antidepressants to which patients have shown an acute treatment response may, appropriately, be continued long-term when the risk of a severe depressive relapse is high (C). They should be used in combination with a medicine showing long-term anti-manic efficacy (C)
- Discontinuation of long-term treatment is not indicated when there is a good clinical control of the illness. When it is necessary, it should be tapered (C). In the case of lithium there is a specific risk of manic relapse if it is discontinued within a 2-week interval (Ia). Poor compliance is a contraindication to lithium because of risk of new illness episodes on discontinuation (Ia)

Key uncertainties

- Successful long-term management often appears to require combination treatment (C). At present, there is little to guide practice other than safety concerns and pragmatic outcomes in individual cases
- The long-term value of antidepressants is not sufficiently established
- Extrapolation of long-term strategies for Bipolar I disorder to Bipolar II or the bipolar spectrum is highly speculative

Mood stabilization is a term used in at least two senses: for reduction in day-to-day variation of mood (a short-term effect of treatment) and for freedom from relapse during long-term treatment. Medicines with putative efficacy against all modes of episodic relapse are sometimes described as mood stabilizers. We do not favour this terminology because available treatments with equal efficacy in the prevention of depression and mania may not yet exist. The long-term use of a wide variety of agents alone or in combination may contribute to mood stability.

At present, the preferred strategy is for continuous rather than intermittent treatment with oral medicines to prevent new mood episodes. This must incorporate additional flexible treatment when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur or anxiety becomes prominent. Higher doses of the long-term treatments or, perhaps more simply, short-term add ons (e.g. benzodiazepines or antipsychotics) will be necessary. Self-medication forms part of the Manic Depression Fellowship's self-management programme, and has proved helpful to a high number of participants (A. Harris, personal communication). Individuals meet with their doctor (when well) to discuss how they might self-medicate in order to prevent, or reduce the severity of a relapse. The focus is often sleep disturbance, so the patient may keep a benzodiazepine or other hypnotic in small supply. Antipsychotics may also be kept on hand with the doctor's agreement, and, if taken at the onset of a manic episode, reduce its severity. It may also be agreed that the patient can increase the dose of their other medicines under specific circumstances. This approach serves two purposes: the individual is more likely to comply with their treatment regime if they feel they have greater control, and they can also take immediate action, when it may otherwise take too long to arrange an appointment with their psychiatrist.

Recent studies have prompted a re-evaluation of the use of the term 'mood stabilizer', implying that an agent will be equally effective against both the manic and the depressive poles of bipolar illness. This form of words may usually be optimistic. While lithium clearly has properties in that direction and in individual cases may be seen to be effective in both senses, on average, it is more effective against the manic pole of the illness. In the case of lamotrigine, the effects are in the opposite direction. We are uncertain of the true magnitude of relevant efficacy against recurrent mania and depression for other medicines used long-term in bipolar disorder simply because there have been insufficient numbers of patients entered into randomized clinical studies. The terminology for 'mood stabilizers' is currently being reworked, but there is not yet a clear consensus whether it will be useful (Ketter and Calabrese, 2002).

Thus, we remain significantly uncertain as to the extent that most medicines used for long-term treatment in bipolar disorder actually do 'stabilize' mood. These include valproate, carbamazepine, gabapentin and topiramate. In the case of the latter two compounds, there is almost no reliable evidence at all favouring their use either in acute mood episodes or to prevent relapse: indeed, for gabapentin it is negative (Ib, Pande *et al*., 2000).

Long-term treatment with lithium and anticonvulsants

There have been adequate numbers of patients randomized into placebo-controlled, long-term or 'maintenance' trials of lithium treatment (Ia, Burgess *et al*., 2001). Relapse rates on lithium over 1 year or so were 40% compared to 61% on placebo. That means in general one would need to treat approximately four patients for 1 year with lithium to avoid one relapse. Because the relative risk reduction remains constant at 33% over 2–3 years, the number you need to treat to avoid one episode of relapse might go down to approximately 2 or 3. The patients who do well on lithium continue to do well on it.

Manic relapse is less common than depressive relapse. However, considering relapse to either pole of the illness individually, there is a 40% relative reduction in risk of manic relapse compared with 23% for depressive relapse for lithium. Lithium is only marginally effective on current evidence at protecting against depressive relapse.

A single RCT of valproate (as valproate semisodium, Depakote®) showed rates for all relapses of 24% against placebo at 38%. This suggests a relative risk reduction of approximately 37%, numerically comparable with lithium but statistically non-significant. The effect for depressive relapse was higher than for mania in this study (Ia, Macritchie *et al*., 2001).

Carbamazepine was the first agent after lithium to be advocated for long-term treatment of bipolar disorder (Ib, reviewed by Okuma and Kishimoto, 1998). It has been re-examined in two recent trials, which showed a substantial benefit to lithium compared to carbamazepine in preventing relapse (Ib, Greil *et al*., 1997; Hartong *et al*., 2003).

Lamotrigine maintenance trials individually support an effect against depression, and only marginally for mania (Ib, outline presentation, GSK) (see below).

Thus, the strongest evidence is still for lithium. It is not based now just on old trials, but also on three relatively recent studies. Lithium certainly prevents manic and probably depressive relapse.

Long-term treatment with antipsychotics

Antipsychotics are often used in bipolar outpatients as long-term treatment. They are prescribed for some patients in depot formulations, as monotherapy or in combination with other agents. The place of antipsychotics is still poorly established because of the limited evidence. The one randomized, placebo-controlled study of a standard antipsychotic in manic-depression did not find

efficacy, and reported some worsening of depressive symptoms (Ib, Esparon *et al*., 1986), although it was inadequately powered.

More positively, some audits of patients on and off depot medications suggest reduced relapse rates for those on antipsychotics without an apparent increase in episodes of depression (IIa, White *et al*., 1993; Littlejohn *et al*., 1994).

Olanzapine has been shown to be effective in a placebo controlled relapse prevention study enriched for acute olanzapine responders and to be superior to lithium as monotherapy after acute response to the combination of lithium with olanzapine (outline presentation, Lilly).

Antipsychotic agents may be appropriate for the long term management of bipolar patients especially where psychotic features are prominent.

Antipsychotics may be useful in difficult-to-treat cases of rapid cycling (III, Lowe and Batchelor, 1986). Clozapine added to usual treatment, principally with lithium or anticonvulsants, was superior to usual treatment alone over 1 year in treatment-resistant bipolar patients, including those with rapid cycling and mixed states. (Ib, Suppes *et al*., 1999)

Long-term treatment with antidepressants

Whether or not antidepressants should be used long-term in bipolar disorder remains uncertain. One small maintenance study (Ib, Prien *et al*., 1984) has been an important influence in this area because it suggested that the treatment of bipolar patients with imipramine alone resulted in an unacceptable number of manic relapses over a 1–2 year follow-up period. This effect was prevented by cotreatment with lithium. It supports the recommendation that monotherapy with an antidepressant will rarely be wise in patients with Bipolar I disorder. The combination of imipramine with lithium was little more effective than lithium alone. This study places a negative perspective on long-term antidepressant treatment, which is incorporated, perhaps uncritically, into North American guidelines.

Long-term treatment of Bipolar I patients with antidepressants is common in clinical practice. Given the significant burden of disease imposed by chronic depressive symptoms and recurrent depressive episodes, this may not be surprising. The evidence supporting the use of antidepressants in the long-term prophylaxis of unipolar depression is unusually strong (Ia, Geddes *et al*., 2003). The equivalent evidence for bipolar patients is almost completely absent. There is non-random evidence for successful long-term prophylaxis with antidepressants in bipolar patients (IIa, Altshuler *et al*., 2001; Ghaemi *et al*., 2001) also receiving combination treatments such as lithium, valproate, carbamazepine and antipsychotics.

The uncontrolled and audit experience of using antidepressants is substantial and, of course, applies to real clinical populations. As Moller and Grunze (2000) have commented, some guidelines for the treatment of acute bipolar depression have gone too far in the restriction of antidepressants.

However, controlled evidence with new compounds is welcome. Two large clinical trials have been completed which compared lamotrigine, lithium and placebo (outline presentation, GSK). In one, the index episode was mania and, in the other, depression. The results from both trials are mutually supportive and show an advantage for lamotrigine in the prophylaxis of depression. There was a comparable advantage to lithium for mania. There was no excess of depressive episodes in lithium treated patients nor manic episodes in lamotrigine treated patients compared to placebo. Indeed for both agents there was a trend towards effects against the opposite pole of the illness. Thus, neither provoked mood instability to the opposite polarity.

Bipolar II patients and, in particular, patients with bipolar spectrum depression have not been sufficiently investigated. Anecdotally, it is possible that effective treatment with antidepressants is possible without an additional anti-manic agent. This is an area that merits further investigation, as the diagnostic issues become more widely understood.

Long-term treatment: winning combinations

For perhaps too long, monotherapy with lithium was believed to be the treatment for bipolar disorder. Increasingly, combinations of agents are being prescribed for the majority of patients who fail on monotherapy. These combinations frequently derive from apparently effective combinations used to control acute symptoms. However, there is little more than anecdotal evidence to suggest that long-term, combination treatment is actually superior to monotherapy. The systematic study of combinations of the currently available medicines appears increasingly necessary. Effective prevention of disease progression may require combination treatment from as early in the illness course as possible. At present, we remain uncertain as to what combination, if any, to recommend from a first episode. It is to resolve these key uncertainties that there is widespread support for large simple trials in bipolar disorder, and such trials require the creation of adequate capacity in the form of collaborative networks of clinicians who can incorporate simple trial methodology into everyday clinical practice (Geddes and Goodwin, 2001).

Suicide

Suicide is a major long-term risk for patients with bipolar disorder. For patients identified by admission to hospital, rates are approximately 10% over long-term follow-up (I, Harris and Barraclough, 1997; Bostwick and Pankratz, 2000). As a rule, suicide is associated with depression, and risk assessment is always emphasized during acute episodes of depression in bipolar patients. However, an equally important perspective is the potential for successful long-term treatment to reduce suicide risk by preventing new episodes or reducing chronic symptoms. Suicide has never been the primary outcome measure for a clinical trial in bipolar disorder, because, in practice, observable rates are too low. However, naturalistic studies suggest that suicide rates are lower in patients who receive long-term treatment (Angst *et al*., 2002). Furthermore, lithium may have particular efficacy. This conclusion is again based primarily on naturalistic comparison of patient cohorts on and off lithium, but the findings from different centres are consistent and the treatment effect is very large (Ia, Tondo *et al*., 2001). One long-term RCT also found suicides and attempted suicides to be associated with carbamazepine and not lithium treatment (Ib, Thies-Flechtner *et al*., 1996).

Adverse effects of long-term treatment

Weight gain is a major problem associated with the use of many of the medicines offered long-term to bipolar patients. Efforts are necessary to alert patients to the need both to maintain normal levels of exercise and moderate calorie intake.

Tardive dyskinesia remains a concern for patients treated long-term with antipsychotics (Keck *et al*., 2000).

Specific psychological interventions in bipolar disorder

- The key components of successful Cognitive behaviour therapy appear to include (Ib):
  - Knowledge or 'psycho-education' with improved evaluation of personal risks posed by the illness
  - Self-monitoring
  - Self regulation: action plans and modification of behaviours
  - Increased adherence to medicines

Key uncertainties

- Whether cognitive behaviour therapy packages can be beneficially introduced during *acute* depressive or hypomanic episodes
- The minimal necessary components to effective psychological intervention

Cognitive behaviour therapy (CBT)

While bipolar patients share many of the common cognitive distortions and attitudes described in unipolar patients (II, Scott *et al*., 2000), a cognitive model is not convincing as a complete theory of the illness. Nevertheless, cognitive theories can fruitfully address some specific problems bipolar patients bring to treatment. Therapy derives pragmatically from clinical experience with bipolar patients (reviewed by Scott, 1996). A preliminary trial in 42 subjects suggested that CBT could speed recovery from depression and prevents the cascade of isolated manic symptoms into full-blown episodes (Scott *et al*., 2001). A formal trial of CBT for currently euthymic bipolar patients has produced important reductions in rates of syndromal relapse, depressive symptoms and manic symptom fluctuation and higher social functioning over a 1-year period compared to treatment as usual (Lam *et al*., 2003). The study targeted patients who were prescribed mood stabilizers and were still suffering from frequent relapses. Compared to treatment as usual, such enhancement of clinical care appears to be very helpful. Treatment includes components of education, motivation to take medicines reliably, self-monitoring, active relapse prevention measures and problem solving. Action plans and modification of behaviours often do not depend solely on the patient to recognize abnormal mood states. Whether the relatively large treatment packages involved in these exploratory studies can be simplified remains to be seen.

Family focused psycho-educational treatment for 21 sessions over 9 months also produced fewer relapses and longer delays before relapse over a 24-month period compared to a brief family psycho-education intervention (two sessions) with as required crisis management sessions. Patients in active treatment also showed greater improvements in depressive (but not manic) symptoms and increased medication adherence. As predicted, the effect was stronger in families with high levels of expressed emotion (Ib, Miklowitz *et al*., 2000).

Resources for complex psychotherapy are always likely to be limited and provision is likely to be most efficient using a stepped approach to care. It seems logical that patients with particularly severe personal and social disturbance may benefit proportionally more from intensive approaches than less challenged patients for whom a lighter touch may be sufficient.

Trials of psychological treatment have for the most part involved intensive input by highly trained and experienced therapists. Whether successful long-term management requires top up of such psychological inputs, or whether it is adequate to maintain a dilute version in outpatient care, is also highly relevant for service delivery.

Treatment in special situations

Elderly patients

Patients with bipolar disorder grow old and older people may develop bipolar disorder *de novo*. Indeed, up to 10% of cases develop bipolar disorder over the age of 50 years, an increasing number as population longevity increases (Sajatovic, 2002). The treatment follows the same principles as for other patient groups, although there is a paucity of studies directed specifically at the elderly. As a group, they are more prone to side-effects due to increased end organ sensitivity, reduced circulation and reduced renal clearance. This may be especially the case with lithium (Sproule *et al*., 2000). In general, treatment doses are lower than those used in younger adults and should be more carefully titrated (Naranjo *et al*., 1995).

Bipolar disorder and pregnancy

The potential benefits of compliance with long-term treatment during pregnancy for a mother with bipolar affective disorder are to remain free of symptoms, enjoy normal bonding with her child and facilitate neonatal development. Failure to control symptoms will risk harm to the mother/child relationship directly or via comorbid alcohol, drug and nicotine consumption. Against the benefits there are some risks. These include teratogenesis, neonatal side-effects reflecting drug toxicity and withdrawal effects.

The risk of major congenital malformations in the general population is surprisingly high at 2% to 4% and increases with maternal age. Cohort studies indicate that this risk is increased to 4% to 12% in lithium-exposed babies (I, Cohen *et al*., 1994), 11% in valproate-exposed babies (II, Kaneko *et al*., 1999) and 6% in those exposed to carbamazepine (II, Rosa, 1991). Although all three medicines are associated with an increased risk, the great majority of women who conceive while taking them will deliver a normal baby.

Previously, lithium's 'specific association' with Epstein's anomaly was believed to represent a high risk. Recent analysis suggests that first trimester exposure to lithium is actually associated with a 0.05% to 0.1% risk of cardiovascular anomalies (a low absolute risk but still higher than in the general population) (I, Cohen *et al*., 1994). Carbamazepine and valproate are associated with a range of congenital abnormalities including neural tube defects (incidence 1% with carbamazepine and 1% to 2% with valproate) (Omtzigt *et al*., 1992) and the foetal hydantoin syndrome (facial dysmorphobobia, cleft lip and palate, cardiac defects, digital hypoplasia and nail dysplasia). The risk of congenital abnormalities is dose-related with valproate (blood levels over 70 µg/ml are implicated) and increases with the number of anti-epileptic agents prescribed (II, Samren *et al*., 1999).

Many of the risks for bipolar patients may be unavoidable because population figures of 30% are given for unplanned pregnancy and this rate may be higher again in patients with mania. Most of the danger for organ development is in the first 2 months and this may be before a woman is actually aware that she is pregnant. Consequently, all female patients of childbearing age should be advised about the importance of effective contraception (Ib, Smith and Whitfield, 1995). Pregnancy should be planned in consultation with the psychiatrist and include a full explanation of

the treatment options and their risks and benefits. Treatment options include continuing the existing medication throughout pregnancy, switching to alternative medicines associated with lower foetal risk before conception, withdrawing some or all medication before conception and reintroducing it either after the first trimester or immediately after birth. The chosen option will depend on the patient's past history and the patient and clinician's preferences. If lithium or valproate is continued during pregnancy, prescribing slow-release formulations twice or more times daily can minimize high peak levels. Some authorities consider withdrawal or reduction of lithium before (planned) delivery and re-establishing the original dose as before pregnancy immediately after delivery.

Patients prescribed lithium, valproate or carbamazepine during the first trimester should be advised about prenatal diagnosis and offered maternal alpha-foetoprotein screening and a high resolution ultrasound scan at 16–18 weeks of gestation. Folate supplementation is advised for all pregnant women but it is unclear whether this reduces the increased risk of neural tube defect associated with carbamazepine and valproate.

Maternal physiological changes during pregnancy may necessitate dosage adjustments. For example, the glomerular filtration rate increases during pregnancy causing many medications to be excreted more rapidly. As a result, serum levels may fall and the mother may require higher doses to prevent a relapse. After birth, these changes reverse and there is a risk of higher serum levels causing side-effects unless doses are reduced. These issues are most relevant to lithium given its low therapeutic index.

ECT can be safely administered to pregnant women.

If patients are taking medicines up to childbirth, both toxic effects and withdrawal effects have been described in clinical case reports/series, although proving causality is often difficult (Ebbesen *et al*., 2000). Vigilance in caring for babies of mothers taking psychotropic agents is recommended.

Breastfeeding requires an understanding by patients of the potential risks of toxicity to the neonate and the need for vigilance in their care. All maternal drugs enter breast milk but the ratio between infant and maternal plasma levels varies greatly. The rate of adverse effects attributable to maternal psychotropic medicines is most uncertain and depends upon sporadic reports (e.g. for example, toxicity due to lithium, hepatic dysfunction due to carbamazepine and thrombocytopaenia or anaemia attributed to valproate). These risks need to be balanced against the benefits of breast feeding (Ia, Austin and Mitchell, 1998). Due to its narrow therapeutic index, lithium is generally regarded as being a relative contraindication to breast feeding (Ia, Chaudron and Jefferson, 2000).

Post partum relapse of bipolar disorder

Childbirth increases the risk of relapse in patients with bipolar disorder in the post partum period. It might be expected to increase admission rates. In fact, this effect is most striking for first psychiatric admissions (I, Terp and Mortensen, 1998). Compared with the admission rate among non-puerperal women in the general Danish female population, the relative risk of all admissions was only slightly increased, RR = 1.09 (95% CI 1.03–1.16) while the admission rate for first admissions was highly increased, RR = 3.21 (95% CI 2.96–3.49). Interestingly, the admission rate for readmissions was reduced, RR = 0.66 (95% CI 0.61–0.72). These risks are less increased than those previously derived from less representative studies.

The relative risk of suicide (and infanticide) is also increased post-partum for women who require admission to psychiatric hospital, although the absolute risk of 1 in 112 for suicide remains absolutely low (I, Appleby *et al*., 1998). It may be misleading, therefore, to imply that suicide is predictable by clinical assessment. Representative figures for the risk of less severe relapse of women with bipolar disorder managed post-partum in the community are not available. Some will be at high risk of relapse. The appropriate strategy is the maintenance or initiation of appropriate medical treatment and good clinical care.

Note

Enquiries about data held by companies and referenced here should be referred to the medical department of the relevant company.

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Appendix

Additional information about medicines

For newer agents (the atypical antipsychotics), clinicians should rely on company data sheets and emerging evidence. Only olanzapine (as Zyprexa®) of the atypicals is currently licensed for acute mania in the UK (second quarter, 2003).

Unexpected adverse effects in bipolar patients should be reported to the relevant licensing authority. There is much accumulated experience to guide the use of lithium. Nevertheless, it is potentially toxic and there is an important potential for litigation if accepted procedures are not followed. Experience with the anticonvulsants is growing in bipolar patients but is extensive from the epilepsy field.

Lithium

Initial workup

- General medical history, physical examination and weight
- Blood creatinine levels (and perhaps creatinine clearance), thyroid function
- Pregnancy test if indicated

Dosing

- Lithium is usually best given as a single dose at night. The commonest dose for younger patients is 800 mg, which can be tapered in at the clinician's discretion
- Titrate dosage further upward if necessary (generally to serum concentrations of 0.5–1.0 mEq/l) according to response and side-effects
- Check lithium level after later dosage increases (steady-state levels are likely to be reached approximately 5 days after a dosage adjustment)
- The 'optimal' maintenance level is the highest dose tolerated without significant side-effects. It will vary from patient to patient
- Older patients, and others with reduced renal function, will require lower doses
- In acute mania, higher serum levels (1.0–1.5 mEq/l) are claimed to be more efficacious, but clinical vigilance is required for adverse effects

Long-term monitoring of laboratory values

- Serum lithium levels should be checked every 3–6 months in stable patients and whenever the clinical status changes
- Renal and thyroid function should be checked every 12 months in stable patients or whenever the clinical status changes

Side-effects

- Side-effects include tremor, polyuria, polydypsia, weight gain, cognitive problems, sedation or lethargy, impaired coordination, gastrointestinal distress, hair loss, benign leukocytosis, acne and oedema
- The common side-effects can usually be reduced or eliminated by lowering the lithium dose or changing the dosage schedule
- With long-term lithium treatment (> 10 years), 10% to 20% of patients display morphological kidney changes. These changes are not generally associated with renal failure, although there are case reports of renal insufficiency attributed to lithium
- Fluid restriction is contraindicated. Troublesome polyuria can be reduced by amiloride (check other electrolytes)
- With elevated thyroid-stimulating hormone, consider adding L-thyroxine
- For persistent tremor, consider adding propanolol
- Most patients experience toxic effects with levels above 1.5 mEq/l; levels above 2.0 mEq/l are associated with life-threatening side-effects and require urgent treatment: haemodialysis may be needed to minimize toxicity
- Lithium toxicity should also be suspected at 'therapeutic' levels in compromised patients with relevant symptoms

Lithium discontinuation

- Abrupt discontinuation of lithium provokes manic relapse in Bipolar I patients (50% in the next 12 weeks). Accordingly, lithium should always be tapered over at least 2–4 weeks, except in medical emergency or overdose

Valproate

Initial workup

- General medical history with special attention to hepatic, haematological, and bleeding abnormalities, physical examination and weight

Liver function tests

- Pregnancy test in women of childbearing age
- Earlier estimated risks for development of polycystic ovarian syndrome appear to have been misleading for valproate (Duncan, 2001)

Dosing

- Valproate semisodium contains a higher fraction (approximately 30%) of the valproate moiety than sodium valproate and dosing should reflect this when switching between agents
- Doses will be given for valproate semisodium because almost all the controlled data was obtained with this formulation. For hospitalized patients with mania, divalproate semisodium can be administered at an initial dosage of 20–30 mg/kg per day in inpatients. A valproate level between 50 and 125 μg/ml has been associated with acute response
- For outpatients, elderly patients, or patients with hypomania or euthymia, start at 500 mg valproate semisodium nocte. Titrate the dose upward by 250–500 mg/day every few days, depending on side-effects. The data sheet suggests divided doses but, in practice, a single dose can often be given at night. The maximum adult daily dosage is 60 mg/kg per day but all patients receiving daily doses higher than 45 mg/kg should be carefully monitored. However, a total dose of 1250 mg per day is the highest that is usually well tolerated by outpatients

Long-term monitoring of laboratory values

- Repeat liver function tests may be indicated in the first 6 months of treatment, although clinical vigilance is more important. Severe reported complications have occurred early in treatment and usually in children in treatment for epilepsy

Side-effects

- Common dose-related side-effects of valproate include gastrointestinal pain, benign hepatic transaminase elevations, tremor and sedation
- Patients with past or current hepatic disease may be at increased risk for hepatotoxicity
- Mild, asymptomatic leukopaenia and thrombocytopaenia occur less frequently and are reversible on drug discontinuation
- Other side-effects include hair loss, increased appetite, and weight gain
- Rare, idiosyncratic, but potentially fatal adverse events include irreversible hepatic failure, haemorrhagic pancreatitis and agranulocytosis; patients should contact their physician immediately if severe symptoms develop

Drug interactions

- Valproate displaces highly protein-bound drugs from their protein binding sites. Dosage adjustments will be needed
- Valproate inhibits the metabolism of lamotrigine which must be initiated at half the usual dose when added to valproate. Accordingly, lamotrigine dosage should be reduced when valproate is added to it

Carbamazepine

Initial workup

- General medical history with special attention to blood dyscrasias or liver disease
- Full blood count (CBC) with differential and platelet count, liver function tests and creatinine
- Serum electrolytes in the elderly, who may be at higher risk for hyponatraemia

Precautions

- A particular concern with carbamazepine is drug–drug interactions. Induction of enzymes can reduce the effectiveness of coprescribed medications, including antipsychotics, antidepressants and oral contraceptives

Dosing

- Carbamazepine is usually started at a dose of 400 mg nocte for outpatients with acute mania
- In hospitalized patients with acute mania, the dosage may be increased in increments of 200 mg/day up to 800–1000 mg/day or higher if tolerated
- Maintenance dose ranges from 200–1600 mg/day in routine clinical practice and should be as high as possible without producing adverse effects

Long-term monitoring of laboratory values

- CBC, platelet, and liver function tests may be performed during the first 2 months of treatment
- Monitoring is less important than clinical vigilance for potentially serious adverse effects (see below)

Side-effects

- The most common dose related side-effects include fatigue, nausea and neurological symptoms, such as diplopia, blurred vision and ataxia
- Less frequent side-effects include skin rashes, mild leukopaenia, mild liver enzyme elevations, mild thrombocytopaenia, hyponatremia and, less commonly, hypoosmolality
- Rare, idiosyncratic, but serious and potentially fatal side-effects include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, Stevens–Johnson syndrome, toxic epidermolysis and pancreatitis
- Awareness of the possible significance of fever, sore throat, rash, mouth ulcers, bruising or bleeding is essential in view of the rare but severe adverse effects. Patients should be encouraged to seek urgent medical attention if they occur
- Other rare side-effects include systemic hypersensitivity reactions, alopecia, cardiac conduction disturbances, psychiatric symptoms including sporadic cases of psychosis and, very rarely, renal effects, including renal failure, oliguria, haematuria and proteinuria
- The carbamazepine analogue oxcarbazepine may be a useful alternative to carbamazepine based on its superior side-effect profile

Lamotrigine

Dosing

- Lamotrigine should be tapered in slowly and starter packs are available for this purpose, giving 25 mg/day for the first 2 weeks, then 50 mg for weeks 3 and 4. Subsequently, 50 mg/week can be added as clinically indicated up to doses of 400 mg
- In patients who are receiving valproate, or other inhibitors of hepatic metabolism, the dose or the dosage schedule should be halved (i.e. 12.5 mg/day or 25 mg every other day for 2 weeks, then 25 mg daily for weeks 3 and 4)
- Concurrent carbamazepine treatment, or other inducers of hepatic metabolism, will lead to increased metabolism of lamotrigine and will require that dosing be doubled

Side-effects

- The most serious early risk is a rash, associated influenza-like symptoms and hypersensitivity. There have been reports of progression to Stevens–Johnson syndrome and toxic epidermal necrolysis. In early clinical trials with patients with epilepsy, rapid titration of lamotrigine dosage was associated with an incidence of approximately 0.3% in adults and approximately 1% in children

- A slow dosage titration schedule (as above) has reduced the risk of serious rash in adults to 0.1% (comparable to other anticonvulsants)
- Patients should be informed of the risk of rash and of the need to contact the psychiatrist or primary care physician immediately, if any rash occurs
- At rash onset, it is difficult to distinguish between a serious and a more benign rash, but lamotrigine should always be discontinued. If the rash is trivial and disappears, lamotrigine can be tapered in even more slowly
- If rashes are accompanied by fever or sore throat, are diffuse and widespread, or show prominent facial or mucosal involvement, all possible provoking agents should be stopped and reintroduction should be extremely cautious if attempted at all
- Rash may be more likely if lamotrigine and valproate are administered concomitantly, primarily because the half-life of lamotrigine is effectively doubled or tripled due to the effects of valproate effects on hepatic metabolism