

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

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Consensus Group of the British Association for Psychopharmacology

Abstract

The British Association for Psychopharmacology guidelines specify the scope and target of treatment for bipolar disorder. The second version, like the first, is based explicitly on the available evidence and presented, like previous Clinical Practice guidelines, as recommendations to aid clinical decision making for practitioners: they may also serve as a source of information for patients and carers. The recommendations are presented together with a more detailed but selective qualitative review of the available evidence. A consensus meeting, involving experts in bipolar disorder and its treatment, reviewed key areas and considered the strength of evidence and clinical implications. The guidelines were drawn up after

extensive feedback from participants and interested parties. The strength of supporting evidence was rated. The guidelines cover the diagnosis of bipolar disorder, clinical management, and strategies for the use of medicines in treatment of episodes, relapse prevention and stopping treatment.

Key words

antidepressants; antipsychotics; bipolar disorder; CBT; depression; evidence-based guidelines; lithium; mood stabilizers; treatment

Introduction

The first BAP guidelines for bipolar disorder were published in 2003 (Goodwin, 2003). This is a substantial revision of that original document. However, where consensus remains as it was, the references in this review have not been systematically revised. We have attempted to establish points of genuine cur-

rent consensus. Where there is no consensus, discussion can only highlight the differences not resolve them.

Guidelines are systematically derived statements that are aimed at helping individual patient and clinician decisions. The principal recommendations given here usually apply to the *average* patient. They need to be graded according to the strength of the evidence from appropriate, preferably randomised trials. Such recommendations may be expected to apply

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about 70% of the time so we have used expressions like ‘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 recognise 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 in practically all circumstances. 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 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 consistent with the likely outcomes.

Methodology

This document is the result of an initial meeting held on 18th May 2007. Brief presentations were made on key areas in which new data has become available, with an emphasis on systematic reviews and randomised controlled trials (RCTs). These were 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 together with recommendations and their strength, based on the level of evidence, were circulated to participants and other interested parties. 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 primarily from MEDLINE and EMBASE searches.

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.*, 1999b).

Evidence categories

Evidence categories are developed from Shekelle, *et al.* (1999a).

Categories of evidence for causal relationships and treatment

- I evidence from meta-analysis of RCTs,^a at least one large, good quality, RCT^a or replicated, smaller RCTs^a
- II evidence from small, non-replicated RCTs,^a at least one controlled study without randomisation or evidence from at least one other type of quasi-experimental study
- III evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies
- IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Proposed categories of evidence for non-causal relationships

- 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^b recommendation from category I evidence

^a RCTs must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition although for psychological treatments this may not be met.

^b Extrapolation may be necessary because of evidence that is only indirectly related, covers only a part of the area of practice under consideration, has methodological problems or is contradictory.

- C directly based on category III evidence or extrapolated^b recommendation from category I or II evidence
 D directly based on category IV evidence or extrapolated^b recommendation from category I, II or III evidence
 S standard of good practice

A particular conflict in these and other guidelines arise 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. There is a relative dearth of informative pragmatic head-to-head comparisons of competing treatment options in bipolar disorder.

Scope and target of the guidelines The content of the guidelines is relevant for all doctors who are treating patients with bipolar disorder. We expect that in most cases these will be doctors who are specialists in psychiatry. However, we have written the guidelines with an eye also 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 summarising 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 summarises the evidence. The structure and content are broadly but not precisely aligned between Parts 1 and 2.

Evidence-based practice means practice underpinned by the knowledge that efficacy of treatment choice has been established against placebo or other relevant comparator. It does not mean practice dominated by evidence that one effective treatment is definitely better than the other. The key to success is cautious prescribing of adequate doses and monitoring positive and negative effects.

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 the accompanying document. Clinical practice guidelines developed by other organisations have also been considered. We have sometimes reached different conclusions from other guidelines.

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 (Table 1)

1. Diagnosis Clinicians should make accurate diagnoses of hypomania, mania and mixed states (S). The Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)) provides the key guidance. 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). Involve others in giving collateral clinical information if possible (S). Case finding can also be made more reliable with a screening instrument like the Mood Disorders Questionnaire (I).

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

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 are highly comorbid with bipolar disorder from a lifetime perspective, and anxiety symptoms are associated with increased illness burden and poor outcome (I); both require assessment and treatment (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 prescribed medications most commonly associated with secondary mania (I).

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

Organic conditions, such as thyroid disease, multiple sclerosis, HIV or any lesion(s) involving subcortical or cortical areas may be associated with secondary mania (II) and should be considered in the differential diagnosis (S). These conditions are most likely in older patients.

The diagnosis of bipolar disorder in childhood is controversial. We favour a narrow definition of the condition, which recognizes unequivocal euphoria and an episodic course as the defining characteristics of a rather rare condition before

Table 1 Fundamentals of patient management

- Diagnosis
- Access to services and safety
- Enhanced care

puberty (II). Irritability should not be treated as equivalent to mood elevation as in adults, since this, and the acceptance of a chronic rather than episodic illness course may lead to an inflation of the number of children receiving the diagnosis (D). Nevertheless, irritability is almost invariably associated with the diagnosis even when defined narrowly (II).

Importantly, in many child and adolescent services, bipolar disorder may well currently be under-diagnosed (IV). Thus, the challenge is not to restrict current diagnostic practice but to improve it.

Following puberty, confidence in applying the familiar adult criteria is appropriate. 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 hypomania, mania or a mixed episode*. In the presence of mood elevation, disturbed behaviour should not be attributed solely to personality problems or situational disturbance (B).

A dual diagnosis of bipolar-I or -II and a personality disorder may be appropriate in a significant minority of patients (II). Treatment principles for bipolar disorder still apply (D).

2. 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 an assessment of clinical risk (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). Suicide is associated with male gender, previous attempted suicide, hopelessness at index admission and, perhaps, a family history; it is a particular risk early in the illness course (I).

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

3. Enhanced care

a. Establish and maintain a therapeutic alliance

A doctor should 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 and what is important to them in terms of the illness and its treatment (S).

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

The management of bipolar disorder is often complex and requires long-term treatment (I). Referral to services with a short-term focus or back to primary care after acute episodes is often unhelpful (D).

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 poor insight, 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 (B).

c. Enhance treatment adherence

While respecting patient preferences, education about the illness after an acute manic or mixed episode should emphasize the long-term need for medicines (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 dose or by employing different scheduling (e.g. prescribing all sedative medicines at bed time) or alternative formulations (B).

Consider participation in clinical research and randomized trials of treatment 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 (B).

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

Help the patient, family members, and significant others 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 in patients whose condition has been effectively stabilized (S). Patients' relatives should feel comfortable contacting the clinician to report escalations of symptoms or other emergencies (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, manic or even hypomanic 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 reliable information and links to local or national support groups (S).

f. Increase the focus of care planning in women of child-bearing potential

The postpartum is a time of very high risk of relapse or recurrence into severe illness in women with bipolar disorder (I). This high risk must be recognized by psychiatric and antenatal services and should be communicated to all healthcare professionals involved in pregnancy and postpartum care (B). All women at antenatal booking should be asked about a history of bipolar disorder, and pregnant women with a history of bipolar disorder should be under the care of psychiatric services (S). Vigilance and close monitoring during the perinatal period is essential, and effective prophylactic treatment should be considered (B).

In pregnancy, there is a risk of teratogenicity from a number of the medicines used in all phases of treatment (I & II). Higher teratogenic risks appear to be associated with the anticonvulsants (valproate > carbamazepine > lamotrigine) (I & II). Lithium has also been associated with teratogenicity, although prospective studies suggest risk is lower than originally described (II). Lowest risks appear to be associated with the antipsychotics (II & III). However, risks for new compounds are usually unknown and always justify caution.

Many psychotropics can cause symptoms in neonates (II & III). Neonates should be monitored for possible adverse effects following birth (C). Long-term effects on cognitive development have been reported with exposure to valproate in pregnancy (I).

Decisions regarding the use of medication in pregnancy and during breastfeeding need to be taken by women bearing in mind the very high risk of recurrence (A). Discontinuation or switching medicines risks de-stabilizing mood and precipitating relapse (I & II). Any risk putatively associated with the use of medicines should be considered in the context of the relatively high, age-related, background risk for congenital malformations and spontaneous abortion in the general population (S).

Women who continue psychotropic medication after child-birth should choose between breast and bottle feeding after a full explanation of the relevant risks and benefits (C). Factors in the baby, such as prematurity and systemic illness, should also be considered in the risk benefit analysis. If a mother takes medication and breast feeds, then the infant should be monitored for possible adverse effects (S).

Since 50% or more of pregnancies occur unplanned the possibility of current or future pregnancy and issues of contraception should be considered and discussed when prescribing to women of reproductive potential (S). Medications with a high risk in pregnancy such as valproate or carbamazepine (CBZ) should not be used routinely if there is a significant risk of pregnancy (B).

Treatment of different phases of bipolar illness (Table 2)

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

Product licences are primarily designed to limit the actions of companies, not of clinicians. Some products have been licensed for indications other than bipolar disorder, yet good evidence has accumulated for their efficacy in bipolar disorder without a corresponding change in the Summary of Product Characteristics (SPC). Accordingly, 'Off label' prescribing of medicines may be implied by some of the recommendations incorporated below. However, we do not encourage adventurous anecdotal use of medications either alone or in combination. Seek expert advice if unsure about the efficacy or safety of any individual medicine or its use in combination (S).

Table 2 Treatment of different phases of bipolar illness

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

1. Acute manic or mixed episodes (Figure 1)

Choice of an initial treatment

Most patients with mania will require short-term treatment with medicine(s) in an appropriate clinical setting (I). No psychotherapy currently provides an alternative strategy for management. A less noisy and stimulating environment with higher nursing staff-patient ratios (e.g. a Psychiatric Intensive Care Unit) may reduce behavioural disturbance in some patients with mania (D).

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 (S). Do not escalate the dose of antipsychotic simply to obtain a sedative effect (S).

For less ill manic patients, lithium or CBZ 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 pro-

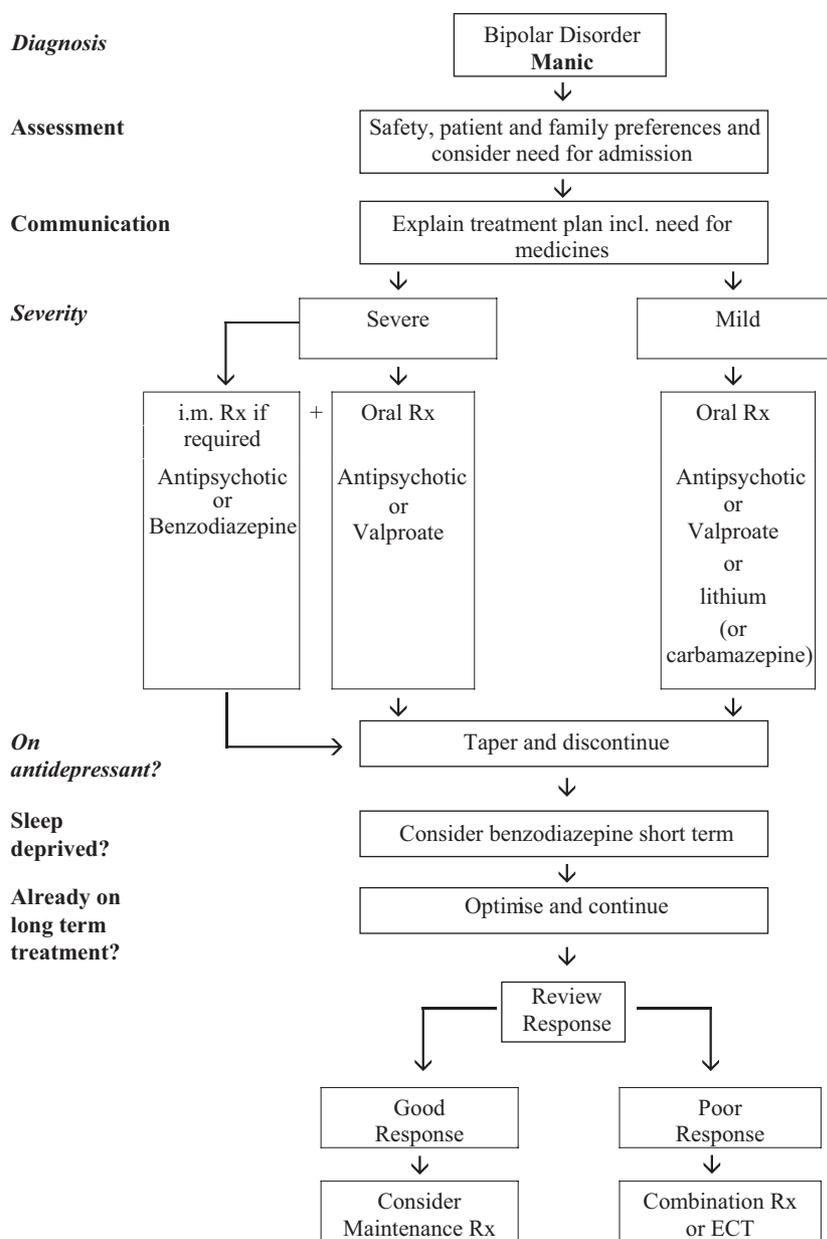


Figure 1 Initial treatment scheme—mania/mixed episode.

file, especially in relation to motor side effects and the 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, CBZ or valproate (I), although long-term usage of atypical antipsychotics has grown substantially.

If the current problem is due to inadequate antecedent symptom control, ensure that the highest well-tolerated dose of the current treatment is offered (A). For lithium, check serum levels are within the therapeutic range (0.5–1 mmole/l); consider establishing a higher serum level within the therapeutic range (B).

Initiate an antipsychotic or valproate, to achieve a combination of medicines from different classes (A).

Consider patient preferences established in previous illnesses or, ideally, in 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 the 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 the episode is associated with 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).

Electro-convulsive 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 in relation to motor side effects (A).

e. Discontinuation of short-term treatments Medicines used solely for acute treatment may be reduced in dose and discontinued (tapering over 2 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 are often used for short-term treatment of mania and may be appropriately continued when long-term treatment is planned (see below) (A).

2. Acute depressive episode (Figure 2)

Choice of an initial treatment

a. For patients not already on long-term treatment for bipolar disorder Where an early treatment effect is desirable, consider quetiapine (A).

Consider initial treatment with lamotrigine, with the necessary dose titration (A).

Treatment with an antidepressant (e.g. selective serotonin reuptake inhibitor (SSRI)) and an anti-manic agent (e.g. lithium, valproate or an antipsychotic) together may be considered for patients with a history of mania (B). Antidepressant monotherapy is not recommended for such patients because of the increased risk of switch to mania (I) and should be used with caution in patients with a history of hypomania (D).

If not already on an antipsychotic, consider adding an antipsychotic when patients have psychotic symptoms (A).

Consider ECT for patients with high suicidal risk, psychosis, severe depression during pregnancy or life-threatening ina-

tion (A). Consider simplifying pre-existing polypharmacy, which may change seizure thresholds. It is very unusual for ECT to be used against a patient's will and fears about this should be allayed (S).

When depressive symptoms are less severe, lithium or possibly valproate may be considered (B).

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

Consider interpersonal therapy, cognitive behavior therapy or family-focused therapy (FFT) when available since these may shorten the acute episode (A).

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, CBZ, valproate, antipsychotic) (A).

If the patient fails to respond to optimization of long-term treatment, and especially if depressive symptoms are significant, initiate treatment as above (or consider augmentation or change of treatment – see Next-step treatments following inadequate treatment response to an antidepressant below) (A).

c. Choice of antidepressant The limited evidence supports the modest efficacy of antidepressants such as the SSRIs (specifically fluoxetine) in bipolar disorder (I). However, antidepressants should not be uncritically employed as first-line medicines given continuing doubts about relative efficacy and their potential to destabilize mood (II).

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 (II).

Tricyclic antidepressants and probably other dual action drugs like venlafaxine (and possibly duloxetine) carry a greater risk of precipitating a switch to mania than other antidepressants (II) and are not recommended except for patients who fail to respond to an initial treatment (C).

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

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

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. In the absence of convincing evidence

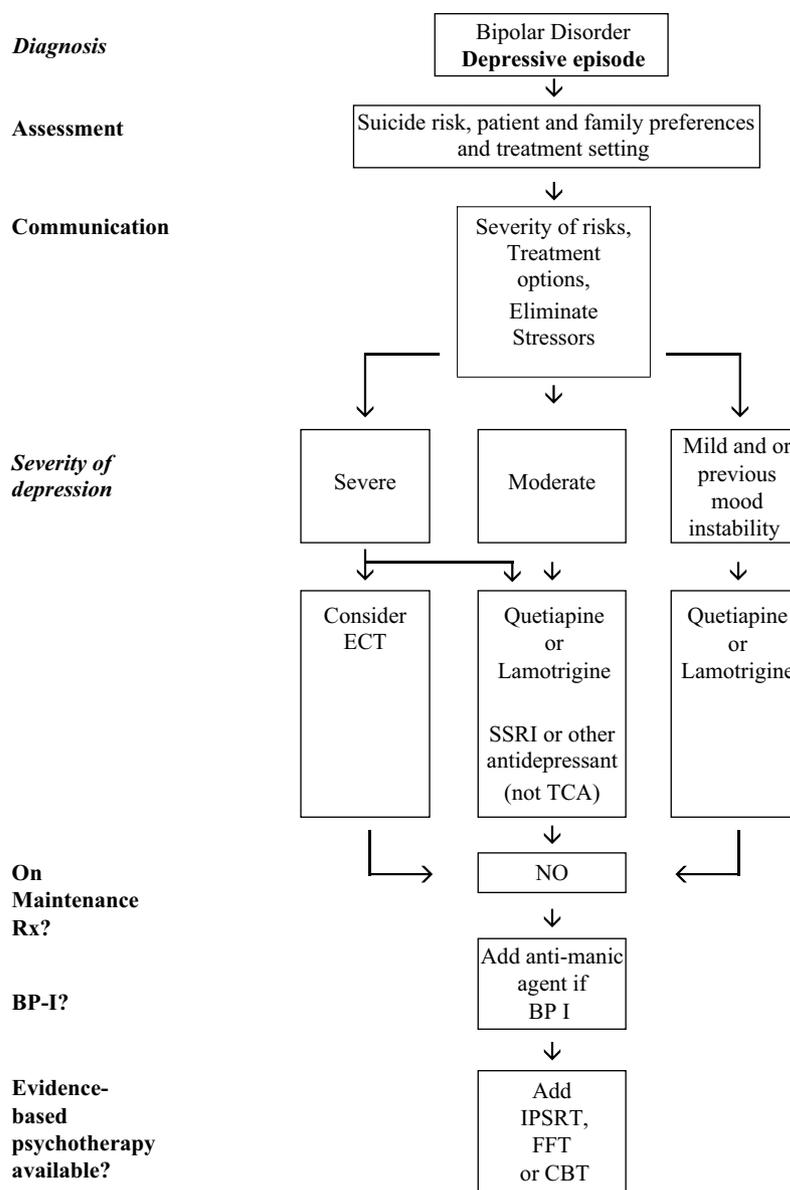


Figure 2 Initial treatment scheme—Depressive episode.

in favour of long-term treatment with antidepressants, the usual policy should be discontinuation (D), although a small minority of patients appears to do well on combination treatment that includes an antidepressant.

e. Next-step treatments following inadequate treatment response to an antidepressant Relative or even marked treatment resistance may occur in depressed bipolar patients (II). Since 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: Next step treatment options).

3. Long-term treatment (Figure 3)

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).

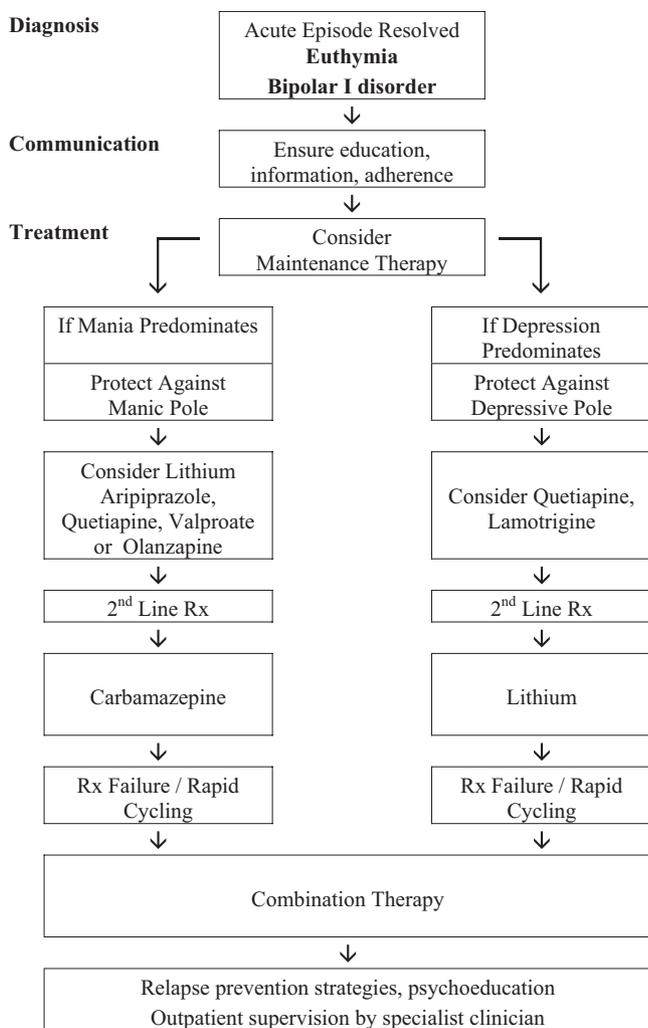


Figure 3 Long term treatment scheme—maintenance therapy.

When a patient has accepted treatment for several years and remains very well, they 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 given increasing evidence for common effects from clinical trials (A).

b. Options for long-term treatment

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 often 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. However, the use of additional short-term medication (e.g. benzodiazepines or antipsychotics) is necessary when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur or anxiety

becomes prominent. Consider supplying short-term medicines prospectively to patients to use with clear advice (e.g. suggest taking for 4 days, but if not settling or getting worse to seek medical attention) (D). Higher doses of the long-term treatments may also be effective, thus avoiding the need for additional medications (D).

Since 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 (I).

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

Consider other options, not necessarily in this alphabetical order, if lithium is ineffective or poorly tolerated:

- Aripiprazole prevents manic relapse (I).
- CBZ is less effective than lithium (I) 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 CBZ (A). Oxcarbazepine may be considered by extrapolation because of its lower potential for such interactions (D).
- Lamotrigine prevents depressive more than manic relapse (I).
- Olanzapine prevents manic more than depressive relapse (I).
- Quetiapine prevents manic and depressive relapse (I).
- Valproate probably prevents manic and depressive relapse (I).

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 (D).

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

When the burden of disease is mania, it may be logical to combine predominantly anti-manic agents (e.g. lithium, valproate, an antipsychotic) (D). When the burden is depressive, lamotrigine or quetiapine may be more appropriate. In bipolar-I disorder, lamotrigine may usually require combination with an anti-manic long-term agent (D).

Lamotrigine and quetiapine may be effective as monotherapy in bipolar-II disorder (II).

The role of antidepressants in long-term treatment is not established by controlled trials, but they appear to be used effectively in a small minority of patients in the long term (II).

Consider clozapine in treatment refractory patients (C).

e. Rapid cycling poses particular long-term management problems because of the associated illness intensity

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).

There is little data on which to base initial treatment beyond extrapolation or secondary analysis of acute and long-term efficacy data for bipolar-I patients in general (B or C). Equally, there is no basis yet for identifying rapid cycling as a particular sub-group requiring a different approach to treatment.

For many patients, combinations of medicines are required (D). 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* (II). Accordingly, if considered, it should be accompanied by an informed assessment of the potential costs and dangers (S).

Discontinuation of any long-term medicine should normally be tapered over at least 2 weeks and preferably longer (A and D). Early relapse to mania is an early risk of abrupt lithium discontinuation (I). Clinical monitoring during treatment withdrawal is desirable (S).

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

g. Specific psychosocial interventions

Psychosocial interventions enhance care, which can increase adherence and reduce the risk of relapse (II). Education is assumed to be a component of good clinical practice because clinical communication cannot be effective without it (S). A large and comprehensive programme of psychoeducation has also been shown to be superior to an equivalent time spent in a nonspecific-talking therapy (II).

There remains concern that generic therapies like cognitive therapy and family therapy should not be offered without clarity that the content reflects the practice of therapists with specialist expertise in bipolar disorder. (D).

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

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

The treatment of women who are or may become pregnant requires greater awareness of the risk benefit considerations highlighted in the section above on enhanced care (3f).

5. Physical health Severe bipolar disorder is associated with poor physical health and potentially with poor access to relevant screening and treatment (I).

It is of growing concern that many of the long-term treatments that appear to be required for bipolar disorder may add to this burden of physical disease (I).

Take all possible steps to protect and improve the physical health of patients in your care through active screening and treatment of risk factors or declared disease (S).

Part 2: consensus points and review

Fundamentals of patient management

1. Diagnosis

- DSM-IV criteria provide the appropriate schema for diagnosis of bipolar disorder. DSM-IV mania defines bipolar-I disorder (S).
- Hypomania, while it must reflect a change in the patient's behaviour which is noticeable to others, is *not* associated with significant functional impairment. With major depression, it defines bipolar-II disorder (I).
- Incidence per lifetime is about 1% for bipolar-I and also about 1% for conservatively defined DSM-IV bipolar-II disorder (I). Bipolar disorder not otherwise specified (NOS) adds a further 2%–3% of bipolar diagnoses in adults.
- Relapse in bipolar-I and bipolar-II disorders occur 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 does not define a stable subgroup but is an important course specifier and may be a particular challenge for treatment (I).
- Hypomania and mania induced by antidepressants should permit the diagnosis of bipolar disorder (IV). This is also the case for stimulants, if mood elevation clearly outlasts clearance of the provoking drug.
- Anxiety disorders and disorders of impulse control are common comorbid conditions in bipolar disorder (I).
- Alcohol use disorders are commonly comorbid with bipolar disorder (I). Substance misuse is more relevant to younger patients with mania (I). Established addictive problems should be independently assessed and treated (S).
- Diagnosis away from bipolar disorder to 'borderline personality disorder' may occur because of the misinterpretation of manic behaviour and is rarely justified (D). Axis II (personality) diagnoses may occur in bipolar disorder but do not necessarily dictate the choice of treatment for the bipolar disorder (D).
- 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).

- Bipolar-I disorder (mania) occurs uncommonly in prepubertal children, but its accurate diagnosis in children and young adults is highly desirable.
- A broad definition of bipolar disorder in prepubertal children is an area of development and current concern.

Key uncertainties

- Severity of mania, presence of psychotic features and the admixture of depressive and manic symptoms may all influence outcome but are poorly characterised in relation to treatment response.
- Mixed episodes form an unstable diagnostic category because the mix of symptoms may vary over time within an episode and the threshold between a syndromal and subsyndromal expression of depression or mania is arbitrary.
- 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 just hypomanic symptoms. The bipolar spectrum so implied has uncertain implications for treatment.
- The diagnosis of bipolar disorder in children is controversial. The incidence described in North America appears to be much higher than in the rest of the world, and the prospectively determined outcomes of children so diagnosed will be of great interest.

Reliable diagnosis was one of the major achievements 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-TR (American Psychiatric Association, 1994, 2002). 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 standardised interviews could ensure improved diagnosis under ordinary clinical conditions (Hiller, *et al.*, 1993).

Bipolar disorder is, at present, 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/year. 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 about three to four people per 100,000/year. Incidence per life-time of bipolar disorder is approximately 0.5%–1% for bipolar-I disorder (I, Angst and Sellaro, 2000; Lloyd and Jones, 2002; Merikangas, *et al.*, 2007).

Bipolar-II disorder is characterised by episodes of hypomania and, invariably, major depression. As currently defined (by DSM-IV), its lifetime incidence is also about 1% (I, Angst, 1998; Merikangas, *et al.*, 2007).

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 in hospitalized samples. The rate of relapse is higher than that seen in unipolar disorder of comparable severity (I, Winokur, *et al.*, 1993) (Angst and Preisig, 1995). Nevertheless, outcomes are very variable and difficult to predict (Kessing, *et al.*, 1998; Kessing and Mortensen, 1999).

The known aetiology of bipolar disorder reveals a complex disorder with both genetic and environmental contributions (I, Potash and DePaulo, 2000). Recent detailed mapping of the human genome has confirmed some specific but small associations with polymorphisms in a number of specific genomic locations (Wellcome Trust Case Control Consortium, 2007; Sklar, *et al.*, 2008). These findings account for very little of the genetic risk imputed from family studies and cannot yet inform diagnosis and treatment choices (Braff and Freedman, 2008).

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, Browne, *et al.*, 2000; Bain, *et al.*, 2000; Lloyd and Jones, 2002). Factors such as early abuse and neglect increase the risks for other comorbid psychiatric disorders and so worsen the course of bipolar illness (II, Leverich, *et al.*, 2002). Abuse and neglect are also associated with impairments of memory and executive function in bipolar patients (Savitz, *et al.*, 2008) and may increase the risk of psychosis (Read, *et al.*, 2005).

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 hospitalisation 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 hospitalisation to prevent harm or 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 clinical 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 present in as many as 50% of manic episodes requiring hospital admission (McElroy, *et al.*, 1996).

In a minority of cases, symptoms seem to be mood incongruent and in some cases this is diagnosed as schizo-affective disorder. Strictly defined schizo-affective 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 schizo-affective diagnosis also remains controversial. It may represent forms of illness in some sense intermediate on a unitary continuum between the two Kraepelinian psychosis types or it may represent a categorical overlap between different disorders (II, Kendell and Gourlay, 1970; Kendell, 1987). Genetic findings are beginning to favour the former explanation (Owen, *et al.*, 2007)

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 in males. However, some significant admixture of dysphoric (depressive) symptoms occurs in many manic episodes. 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 characterised 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-associated mania should usually be regarded as defining bipolar disorder, except when the symptoms are reliably locked in time to exposure to an antidepressant, like other drug-induced psychoses discussed below (IV).

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 recognises 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.

Simple inclusion of bipolar disorder NOS contributes a 2.4% community lifetime incidence (Merikangas, *et al.*, 2007). Bipolar disorder NOS is a DSM-IV category that includes any of the following: (1) recurrent subthreshold hypomania in the presence of intercurrent major depression, (2) recurrent (at least two episodes) hypomania in the absence of recurrent major depression with or without subthreshold major depression and (3) recurrent subthreshold hypomania in the absence of intercurrent major depression with or without subthreshold major depression. The number of required symptoms for a determination of subthreshold hypomania is confined to two criterion B symptoms (from the DSM-IV requirement of 3, or 4 if the mood is only irritable) to retain the core features of hypomania in the subthreshold definition.

A different solution is to define the diagnosis of hypomania 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 submanic 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 they simply redistribute approximately 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 also 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. However, to call such cases bipolar will increase the temptation for treatment choices to be extrapolated from either bipolar-I or bipolar-II data.

On the basis of symptom endorsement over a life time in clinic samples, Cassano and colleagues suggested that mood elevation forms a continuous bridge between unipolar and bipolar disorder (Cassano, *et al.*, 2004). The intensity of illness, either depressive or manic, increased in parallel and simply showed a higher baseline of elated experience for the bipolar group compared to the unipolar cases. Together, these findings have generated interest in how eventually to implement dimensional bipolarity scores into future revisions of the DSM criteria (Vieta and Phillips, 2007)

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 distin-

guished. 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. Indeed, there are a number of other clinical features suggesting a bipolar illness, such as 'atypical' depressive features (hypersomnia, hyperphagia and leaden paralysis), pathological guilt and lability of mood, but none can convey a categorical certainty. There may be scope for the development of such features as a measure of probability that an episode of depression is the manifestation of bipolar disorder in the absence of evidence of mood elevation (Mitchell, *et al.*, 2008; Goodwin, *et al.*, 2008).

Deliberate self harm and completed suicide are important risks in bipolar disorder and are associated with depression and mixed states (I, ten Have, *et al.*, 2002; Black, *et al.*, 1987). Assessment of risk should be as for other depression diagnoses and should follow widely accepted principles of good clinical practice (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. Four is an arbitrary number and not a point of rarity in the distribution of cycle frequencies. The definition also groups together patients with frequent illnesses giving 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 around 16% in clinic populations, and it is weakly associated with female gender, early onset of symptoms, bipolar-II disorder, current hypothyroidism and a poor response to lithium (especially the depressive component) (II-III, 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. There are few follow-up studies over the long term. In the Mental Health Collaborative Depression Study (Coryell, *et al.*, 2003), a rapid cycling pattern was associated with serious suicide attempts. However, in 4 out of 5 cases, rapid cycling ended within 2 years of its onset. Resolutions were not associated with decreases in tricyclic antidepressant use.

Comorbidity Comorbidity of bipolar disorder with a range of other psychiatric conditions poses problems of two diametrically different kinds. First, nonspecific 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). Secondly, in the presence of recognised bipolar disorder, comorbid conditions may contribute to poor treatment response and outcome. Community samples show replicated high lifetime comorbidities of bipolar-I

disorder with a range of anxiety related disorders and substance misuse (I, Kessler, *et al.*, 1997; Merikangas, *et al.*, 2007). Lifetime rates are extremely high: as many as 90% of patients may at some time have had an anxiety disorder (I-II, Freeman, *et al.*, 2002; Merikangas, *et al.*, 2007). Anxiety symptoms as well as disorder are also common in bipolar samples, and the experience of panic and obsessive-compulsive symptoms is associated with poor outcome and illness severity (Fagiolini, *et al.*, 2007). 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. When the anxiety disorder dominates the outcome this must clearly influence evaluations of successful treatments. Anxiety disorder comorbidity is associated with a range of worse outcomes in bipolar disorder (Simon, *et al.*, 2004; Fagiolini, *et al.*, 2007), yet has received little specific attention in developing treatments.

The risk of alcohol dependency is another common and clinically significant comorbidity of bipolar-I and bipolar-II disorders. Drugs, especially stimulants, are more relevant to younger patients with mania and are 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; Brown, *et al.*, 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 adherence and bipolar outcomes (II, Salloum and Thase, 2000).

Bipolar disorder is comorbid with disorders of impulse control. Impaired impulse control will contribute to disturbed behaviour both within and between episodes. Distinguishing between possible explanations for such behaviour in any presentation – mood, personality disorder or impulse control disorder – is clinically challenging.

Organic conditions, such as thyroid disease, multiple sclerosis or any lesion(s) involving 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.

Personality disorder Personality disorder may be an important Axis II accompaniment of bipolar disorder. Although the categorical approach to personality disturbance has important limitations (Blacker and Tsuang, 1992), the clinical employment of personality diagnoses remains rather common. There appears to be an important risk that a personality diagnosis may blind the clinician to bipolar disorder, rather than vice versa. The diagnosis of borderline personality disorder, in particular, seems often to be seen as a differential diagnosis with bipolar disorder. Borderline personality is unlikely (or more likely to be secondary) in the presence of clear cut mania or sustained elation without evident stressors: unfortunately the behavioural excesses of mania may lend themselves to fanciful interpretation of the 'underlying' personality. Repeated anger, deliberate self-harm reactive to interpersonal stress and extreme rejection sensitivity are axiomatic of borderline personality disorder (Gunderson, *et al.*, 2006). Periods of depression and irritability are rarely instructive in the differential diagnosis. However, it is not necessary always to distinguish between the disorders: a dual diagnosis of bipolar-I or II and borderline personality disorder may be appropriate in as many as 20% of borderline patients in clinic samples (II, Gunderson, *et al.*, 2006).

When a patient has both a borderline and a bipolar diagnosis, there is no reason to withdraw or withhold appropriate treatment for bipolar disorder (D).

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 it will be because, as noticed in the previous section, the first developments may be nonspecific 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.

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, as already noticed, 'personality' diagnoses are still perhaps too readily employed (III, e.g. 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 less consequential. 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. In addition to morbidity, the failure to diagnose bipolar disorder appears to incur significant additional costs (McCombs, *et al.*, 2007). 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 (D).

Diagnosis of bipolar disorder in children There is general agreement that bipolar-I disorder as defined by the DSM-IV criteria can present before puberty, should be considered as a differential diagnosis and be diagnosed in children when these criteria are met. NICE Guidance has summarized the position (National Institute for Health and Clinical Excellence (NICE), 2006) as follows: prepubertal mania (implying a bipolar-I diagnosis) is a relatively rare condition and its recognition should rest on the detection of the symptoms of euphoria and grandiosity and not simply irritability. Nevertheless, irritability is almost always present in this age group with mania (Youngstrom, *et al.*, 2008). The condition should be episodic, rather than chronic. The use of DSM-IV criteria was recommended to guide diagnosis, although the best way to operationalize the diagnostic criteria in children (and adolescents) has yet to be determined and remains a source of some controversy. It is quite likely that mania is more often missed and misdiagnosed than it is overdiagnosed in the UK.

Despite reasonable agreement about the bipolar-I diagnosis, there is particular uncertainty surrounding the validity of a broader bipolar diagnosis in prepubertal children. NICE reflected what may be considered to be a European perspective (II, Wals, *et al.*, 2001) by suggesting that a broad definition of bipolar disorder in childhood (including BP-II and BP-NOS) is currently unreliable and unhelpful in most cases.

In North America, by contrast, childhood and adolescent diagnoses of the broader bipolar phenotype have become widely accepted (II, Geller, *et al.*, 1995). Rates of diagnosis of bipolar disorder have increased 40-fold in children and young people in recent years (Blader and Carlson, 2007; Moreno, *et al.*, 2007). In fact, there are major theoretical and practical differences in the way that the broader bipolar phenotype is understood between different academic centres in North America (Youngstrom, *et al.*, 2008; Leibenluft, *et al.*, 2003). The debate is not about whether there is a group of children with extreme emotional lability, and explosive mood dysregulation. All agree that these children are common within clinical practice and are often very challenging to treat. The debate is whether these children are best characterised as suffering from bipolar disorder (McClellan, *et al.*, 2007).

A recent study highlighted the different perspectives of clinicians in the UK and US; those in the UK were similar in their recognition of classic bipolar-I but much more conservative when presented with less clear-cut cases (Dubicka, *et al.*, 2008). Prospective studies to validate the childhood diagnoses are ongoing, although really long-term data in community samples are not yet available (Birmaher and Axelson, 2006; Birmaher, *et al.*, 2006).

The desire to move diagnosis earlier in the life history is entirely understandable. Unfortunately to do so, inevitably risks sacrificing specificity to sensitivity. At the risk of oversimplification, softening the diagnosis of bipolar disorder to allow irritability and chronicity risks confounding with more

common problems such as Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder. Indeed, these disorders are usually described as very commonly comorbid with childhood bipolar diagnoses in US case series, even when the bipolar disorder is narrowly defined (Dickstein, *et al.*, 2004). Affective instability is undoubtedly a component of many troubled children, but whether it allows 'early diagnosis' of true bipolar disorder is uncertain.

A key problem is the lack of quality treatment studies in either child or adolescent samples and the consequent tendency for extrapolation of adult prescribing recommendations to children diagnosed with 'bipolar disorder' on the basis of clinical impression. This must be unwelcome without independent evidence of benefit and, at least safety, from appropriate trials in such children, difficult as they are to conduct.

None of these reservations concerning current practice implies a negative attitude to further research in this area, which is clearly necessary.

2. 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's 'National Service Framework' in the UK implies a current lack of understanding among policymakers of the need for high-quality specialised 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 diagno-

sis, 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 (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 (Harris and Barraclough, 1997).

The apparent neglect of the specific needs of bipolar patients in UK government policy (IV, Morriss, *et al.*, 2002) suggests that 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 United Kingdom (Department of Health, 1999). It has been argued that this is based on a monolithic social model of mental illness, which is inappropriate to bipolar disorder (Goodwin and Geddes, 2007).

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 (I, 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 pharmacological management and accurate assessment of the mental state. This means that a trained psychiatrist should normally be directly involved in patient management.

There is a growing impression that the formal development of expertise in bipolar disorder is an increasingly serious clinical priority in the UK (Goodwin and Geddes, 2007). The provision of this expertise is haphazard and not specifically commissioned in the UK, and training in specialist treatment of bipolar disorder is not formally recognised by the Royal College of Psychiatrists. It is, therefore, unsurprising that patients who do not respond to first- or second-line treatment from general adult psychiatrists or remain a diagnostic uncertainty currently experience a virtual lottery in terms of subsequent treatment.

3. Enhanced clinical care

- Enhancement of patient care can be achieved by structured interventions based on principles derived from behavioural and cognitive psychology (II). This has the potential to complement and inform treatment with medicines, not to 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 uncertainties

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

- There is conflicting evidence on the value of relapse prevention approaches based on cognitive behaviour therapy (CBT).

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 (a component of '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 and their carers knowing what to do, and why, appears usually to be an essential prelude to actually doing it.

One option is to provide a formal group course, the efficacy of which was recently shown in a RCT (II, Colom, *et al.*, 2003). This trial compared psychoeducation with an equivalent group experience in which the content was simply unstructured supportive discussion. The psychoeducation arm addressed negative attitudes and developed key skills in relation to early warning signs, drug adherence and regular daily and social rhythms. It did not just aim to increase knowledge. Nevertheless, patients often request, and much 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/>). Very 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 review, 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 (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 minimised by all possible means. These include dose adjustments, once daily administration (e.g. at bed time) and switching between formulations. Other efforts to improve adherence such as user-friendly packaging, monitoring of pill taking, and 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.

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 (II, Kemp, *et al.*, 1998). Since nonadherence to 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 emphasises 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 (I, Ashcroft, 2000). We believe that participation *per se* in well-designed clinical trials can be 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 over 12 sessions, using individual scripts which access their own experience and enable them to take evasive action, appears to be effective in avoiding new episodes of mania (II, Perry, *et al.*, 1999). The approach was less successful with episodes of depression. It would be interesting to know whether a more dilute approach or one focused uniquely on personal symptom signatures for relapse identification into mania would be more

widely applicable. The involvement of family members is often helpful but must be treated sensitively, since 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 characterised, in part at least, by disturbed biological rhythms that may arise as a consequence of disruptions in social rhythms. The reestablishment of routine and regular activity for those behaviours that occur at least once per week is a primary goal in treatment. These ingredients have not been shown to be specifically more effective than other less focussed care packages, although IPSRT appears to delay recurrences of bipolar disorder (Frank, *et al.*, 2005) and speed recovery from BP depressive episodes compared to comparison conditions (Miklowitz, *et al.*, 2007). IPSRT provides a simple framework for practical advice.

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 but simply by enhancing ordinary clinical care, most obviously by using structured psychological treatment programmes. 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. A state of depression or mania is not an auspicious time to make major life decisions. Furthermore, patients may experience considerable difficulty performing at the level for which their education may have prepared them (II, 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, 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 (I, Arts, *et al.*, 2008). These objective problems in sustaining attention, memory and executive function appear to be made worse by repeated episodes (Clark, *et al.*, 2002; Martinez-Aran, *et al.*, 2004). In other words, they may be a quasi-toxic consequence of the intensity of the illness course. Polypharmacy may also compound the problem (Clark, *et al.*, 2002; Frangou, *et al.*, 2005).

The National Service Framework for Mental Health recognised 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. A preliminary investigation of the families of 86 stable patients showed that caregivers still showed a moderate level of subjective burden. The highest levels of distress related to the patient's hyperactivity, irritability, sadness and withdrawal. The patient's illness had also affected the carers' emotional health and life in general. Poorer social and occupational functioning, an episode in the last 2 years, history of rapid cycling and the caregiver being responsible for medication intake explained a quarter of the variance of the subjective burden (Reinares, *et al.*, 2006). More specifically, and perhaps against the clinical stereotype, a small study (Lam, *et al.*, 2005a) of spouses of bipolar patients reported significantly lower marital and sexual satisfaction when their partners were in a manic phase than when their partners were depressed or asymptomatic. More predictably, these same spouses reported they had significantly less marital and sexual satisfaction when the patients were depressed compared to when they were asymptomatic.

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, mood instability, comorbid anxiety 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 within 8 weeks from their remission) from recurrence (the return of new symptoms after 8 weeks), this is both arbitrary and 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; Kupka, *et al.*, 2007). As already noticed, there are also cognitive distortions similar to those seen in depressive disorder (II, Scott, 1996), neuropsychological deficits that are still largely ignored (Arts, *et al.*, 2008) and a less specific failure to return to expected levels of functioning. 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. There is no current consensus, and little research to inform it, concerning how these outcomes should be measured.

1. Acute manic or mixed episodes

- Antipsychotics, lithium and valproate all have antimanic actions (I or II).
- 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 (I). Doses producing extra-pyramidal side effects (EPS) should only be tolerated for the shortest necessary period of time and, if possible, avoided. Anticholinergic agents can reduce the burden of EPS (I).
- The atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) have shown efficacy in monotherapy placebo-controlled trials in mania (I).
- Atypical antipsychotics are less likely to produce EPS than typical antipsychotics used at conventional doses (I), which is of particular significance in bipolar disorder because of an apparently greater risk of motor side effects, including tardive dyskinesia (TD) (III).
- Combination of an antipsychotic with another antimanic agent appears to facilitate the acute treatment response, especially when patients show break-through mania or only a partial response with the first agent. Aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone

when combined with lithium or valproate, have been shown to be superior to lithium or valproate alone (I).

- Benzodiazepines are useful adjunctive agents and can induce sedation or sleep (II).
- 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 or less 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, Cookson, 2001). They are antimanic not simply sedative. However, placebo-controlled data to show that any older antipsychotic works in mania was very limited (e.g. II, Johnstone, *et al.*, 1988), until recent studies included haloperidol as a comparator. Clinically, we depend heavily upon the evident short-term effect of tranquillization, observable in clinical practice and under trial conditions (II, 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/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 (I, Allen, *et al.*, 2001). In the past, 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. When possible, extrapyramidal side effects 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, Post, *et al.*, 1996).

There is a single pivotal comparison of chlorpromazine with lithium (II, 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 (II-III, 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 in part a hyperdopaminergic state appropriately treated by blockade of dopamine receptors. Accordingly, a series of RCTs have been completed showing the efficacy of atypical antipsychotics as monotherapy compared with placebo in mania. These include studies of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone (I, Smith, *et al.*, 2007b). Aripiprazole, olanzapine and ziprasidone exist in parenteral form for acute use. Ziprasidone is not available in the UK.

Amisulpiride, clozapine, sulpiride and zotepine are also potentially antimanic antipsychotics but lack much formal proof of efficacy.

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 (I, Geddes, *et al.*, 2000). Bipolar patients are probably more likely than patients with schizophrenia to show acute EPS, when treated with comparable doses of antipsychotics (I, Gao, *et al.*, 2008). Naturalistic studies in schizophrenia suggest that acute EPS are predictive of subsequent TD (II, Andrew, 1994). It would follow that antipsychotics less likely to induce acute EPS will be less likely to be associated with TD, but the evidence so far in schizophrenia, while supportive, is not conclusive (I, Correll, *et al.*, 2004).

The trials with atypical antipsychotics show that an antimanic action can be achieved without EPS (II, review 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 established efficacy at doses that do not produce motor effects.

The use of lithium and valproate, and not antipsychotics, as first-line treatment for mania has been emphasised in the United States. This treatment choice avoids the issue of EPS. Initially (Frances, *et al.*, 1998), this was to the exclusion of antipsychotics, which were notionally 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 (review by Licht, 1998). The much improved

evidence base for the use of the atypical antipsychotics and haloperidol has essentially resulted in a convergence of practice and the acceptance of antipsychotics as first-line agents for mania worldwide.

Other factors that influence the choice of antipsychotic include properties like sedation, which may be desirable in the short term but not in the long term and the choice of formulation. The effects of antipsychotics on weight and metabolism are also a topic of increasing concern. While this is of most importance for the long-term and will be reviewed at length below, weight gain is certainly obvious in relatively short-term treatment with olanzapine and quetiapine. Hence, it is a factor that is assuming more prominence in the risk/benefit assessment of both prescribers and patients. Finally, some antipsychotics are available in an intramuscular (i.m.) formulation which may be important for initiating treatment.

It is understandable that for clinical reasons, there is a pressure and a temptation for experts to express preferences for one medicine compared with the other. Such opinions may even have commercial value to companies. Unfortunately, average effects in the artificial context of a clinical trial are a poor basis for confidence. Even when studies are designed to compare one treatment with another, the choice of dose and outcomes are often controversial and the differences are modest. This is certainly the case in acute mania.

Other antimanic medicines: lithium, valproate and CBZ

Acute trials support the use of lithium, CBZ and valproate in mania (II, Smith, *et al.*, 2007b). In severe or highly active states, lithium appeared to be less effective than chlorpromazine (II, 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 noncovalent 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*. See Annex for information on dosing of different formulations.

Valproate semisodium has been shown to be effective in severe mania (II, Macritchie, *et al.*, 2003), when the dose should be titrated upwards quickly to control symptoms: 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).

CBZ has antimanic efficacy (II, Okuma and Kishimoto, 1998) but is rarely advocated for first-line treatment. An extended release formulation of CBZ at doses from 400 mg

titrated to 1600 mg (divided doses) has now been shown to have an early antimanic effect in two placebo-controlled trials (Weisler, *et al.*, 2006).

Oxcarbazepine is sometimes employed as an alternative to CBZ: it does not cause autoinduction or as much heteroinduction as CBZ, so is less problematic in its interactions with other drugs (Baruzzi, *et al.*, 1994). While both are anticonvulsants, the mechanism of antimanic action is not established for CBZ. Efficacy has not been formally established using adequate methodology for oxcarbazepine; indeed, a recent study in young people with mania showed no benefit compared with placebo (Wagner, *et al.*, 2006).

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 optimise the maintenance treatment and add an antipsychotic agent. Evidence is available for aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone that, when combined with lithium or valproate, the combination may, indeed, be superior to monotherapy with lithium or valproate in acute mania (II, Bowden, 2005; Smith, *et al.*, 2007a).

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*, and so in preference to antipsychotic monotherapy. This may be rational when there is a wish to spare the antipsychotic dose (II, 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 (II, Sachs, *et al.*, 2002).

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. Lithium in particular is sometimes difficult to use in exhausted, dehydrated patients. When mania can be treated with a monotherapy in its early stages this appears to be preferable to automatic prescription of a combination.

CBZ is not the optimal partner for combination therapy because its liver enzyme-inducing properties may reduce the levels of other agents, which may, in turn, inhibit the catabolism of CBZ (I, 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 tranquillisation 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.

Finally, efforts in acute episodes of treatment 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 than treatment with lithium or valproate to result in patients switching from mania into depression. 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. The data from the lamotrigine/lithium/placebo maintenance trials are a reminder that the risk of relapse of the index episode will usually be higher than the risk of switching (Goodwin, *et al.*, 2004).

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 (Mizrahi, *et al.*, 2007).

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 (D).

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 (II, Bowden, *et al.*, 1994), cases with 'psychotic' and 'classic' mania showed equal valproate and lithium response rates (II, 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), since it may have arisen by chance and will then be misleading. A proportion of patients entering the study were already known to be nonresponders to lithium, which may also have influenced the results.

Secondary analysis of pooled data from acute efficacy trials of antipsychotics has suggested that effects in clinical subgroup are of similar average size (Baldessarini, *et al.*, 2003). However, 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 than to placebo (Baker, *et al.*, 2004). Since olanzapine and quetiapine have been shown to have effects on acute mania and acute bipolar depression, it may seem logical to use them or other medicines with this profile in mixed states. Aripiprazole, despite an absence of proven effect in bipolar depression, may also have efficacy in mixed states (Suppes, *et al.*, 2008).

There is no indication to either 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.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) may be considered for manic patients who are severely ill and/or whose mania is treatment resistant (including mixed states (Valenti, *et al.*, 2008)), 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). In view of the polypharmacy common in bipolar disorder, vigilance is required because fit thresholds may be lowered and the potential for prolonged seizures increased, or raised and seizure induction compromised.

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

2. Short-term treatment of depressive episodes

- Quetiapine has the most convincing RCT profile for bipolar depression (I).
- Lamotrigine has evidence for acute efficacy (I).
- Antidepressants are probably effective for treating depression in bipolar disorder (I).
- Severe depression in a bipolar-I illness course should, when treated with an antidepressant, require another agent that will reduce the risk of mania (lithium, valproate or an antipsychotic) (B).
- The risk of a switch to mania is greater for tricyclic antidepressants or other dual action medications like venlafaxine compared with SSRIs in particular, II.

- While unlikely to provoke a manic switch, lithium, valproate and CBZ have inadequate evidence for acute antidepressant efficacy.
- 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.

Antipsychotics in depression

Interest in the use of atypical antipsychotic agents to treat bipolar depression as monotherapy began when a large RCT showed that olanzapine has a modest antidepressant effect in bipolar-I depression compared with placebo (Tohen, *et al.*, 2003) and previous work had shown that antipsychotics have a place in the management of psychotic depression (II, Johnstone, *et al.*, 1988). The real advance has come from investigation of the efficacy of quetiapine (Weisler, *et al.*, 2008). At doses of 300 and 600 mg, it appears to produce a large and early attenuation of depressive symptoms in bipolar patients compared with placebo. Pooled analysis of two trials, together randomizing nearly 1000 patients, showed effects in bipolar-I and bipolar-II participants (with slightly lower response rates to active treatment in the latter subgroup).

These short-term findings seem likely to increase the use of quetiapine for bipolar depression. The current uncertainties relate to the dose – even 300 mg produces substantial rates of somnolence and sedation, with associated drop out from treatment – and the longer term risks of metabolic disturbance. Even over 8 weeks there is evidence of weight gain and significant increases in triglycerides and blood glucose. While not of great importance in short-term treatment, these changes are an important signal to alert clinicians to the need for monitoring and treatment of such problems in the medium to long term. There are important differences between different antipsychotics and quetiapine appears to lie at the more problematic end of the spectrum (Meyer and Koro, 2004).

Quetiapine may have unusual properties, and the findings in depression cannot be extrapolated to other atypical antipsychotics. Certainly, the effect of olanzapine was less impressive (inferior to adding fluoxetine, as already noted) and two trials of aripiprazole in bipolar depression have failed (Thase, *et al.*, 2008), despite its apparent efficacy in augmenting the action of SSRI treatment in treatment-resistant unipolar depression (Shelton and Papakostas, 2008). One current preliminary sug-

gestion is that an active metabolite norquetiapine, formed by *N*-dealkylation, binds with moderate affinity to the noradrenaline transporter (like many antidepressants) (Goldstein, *et al.*, 2007). This may contribute to quetiapine's antidepressant action.

If norquetiapine is the main active antidepressant agent, there are implications which follow from the polypharmacy common in bipolar disorder. The nor-alkylation is conducted primarily by CYP3A4. This enzyme may not only be inhibited but also be induced (<http://medicine.iupui.edu/flockhart/table.htm>). Relevant agents that will block *N*-alkylation include fluvoxamine and norfluoxetine and inducers include CBZ, modafinil and St John's Wort. Thus, fluvoxamine increases quetiapine levels by 159%, while CBZ can reduce quetiapine levels by 86% (Castberg, *et al.*, 2007); effects on norquetiapine levels would be in the opposite direction.

Antidepressants

Meta-analysis suggests that conventional antidepressants (imipramine, fluoxetine and tranylcypromine) are, on average, superior to placebo in the acute treatment of bipolar depression (I, Gijsman, *et al.*, 2004). However the number of studies and the numbers of patients in the studies are low. In contrast, there has been a very large number of trials examining the efficacy of many different antidepressants in unipolar major depression (I, Anderson, 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 aggregated data for several agents may support an antidepressant action for antidepressants in general, but the evidence for any single agent is very limited. The largest single trial compared the combination of fluoxetine with olanzapine (OFC) and showed a statistically significant benefit. Notwithstanding the positive OFC study, the presence of concomitant mood stabilisers in trials of antidepressants may reduce the probability of finding an effect. The Systematic Treatment Enhancement Program (STEP-BD) study is the largest of such studies and used paroxetine and bupropion against placebo: the results were resoundingly negative (Sachs, *et al.*, 2007). However, whether effectiveness trials which include as much 'consumer preference' as STEP-BD can be expected to demonstrate efficacy appears to be questionable. A full discussion is beyond the scope of this review.

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 suggests consideration of 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 United States, 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.

The status of suicidal or para-suicidal acts associated with antidepressant treatment has been controversial in recent years, but largely confined to cases of unipolar depression. There is a consensus that the risks of real danger have been overstated (Moller, *et al.*, 2008). Bipolar depression has not often been included in the debate although it is sometimes speculated that adverse behavioural effects may be the result of inducing mixed states in undiagnosed bipolar patients with depression, especially in younger age groups. The onset of suicidality in bipolar patients was not associated with the use of antidepressants in the STEP-BD study, although numbers were small and the age group may not have been optimal to demonstrate an effect (Bauer, *et al.*, 2006c). Further evidence will be welcome.

Lithium in depression

Treatment guidelines (Sachs, *et al.*, 2000) have repeatedly suggested 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 (II, Bhagwagar and Goodwin, 2002). Even in maintenance treatment, its efficacy specifically against depression is coming to be questioned (see below). It remains, nevertheless, a useful comparator for new studies in bipolar disorder. In preliminary reports of the EMBOLDEN I trial conducted by AstraZeneca, lithium did not separate from placebo, while two doses of quetiapine did (Young, *et al.*, 2008).

Anticonvulsants in depression

CBZ and valproate have an inadequate evidence base in acute depression, despite recommendations to use them. Lamotrigine had one published study, which suggested benefits in bipolar depression compared with placebo (Calabrese, *et al.*, 1999) and a second study was also supportive (III, Frye, *et al.*, 2000). Four previously unpublished trials conducted by GSK individually failed to show a separation from placebo. Meta-analysis of all five trials was, nevertheless, able to show a modest benefit for lamotrigine in bipolar-I and bipolar-II patients with acute depression (I, Geddes, *et al.*, 2009). This finding supports the use of lamotrigine as a first-line agent for bipolar depression. The failure of the individual trials is instructive. Clearly, placebo-controlled trials permitting early drop-out will disfavour any treatment requiring slow dose titration:

6 weeks was required to reach the likely effective dose of 200 mg in these trials. The trials can simply be described as underpowered, given this problem. However, in addition, analysis of the patients with HAM-D scores at baseline of 24 and above shows a substantial effect on pooled analysis and in two of the individual studies. By contrast, patients who entered with scores below 24 simply showed too high a placebo response to allow a detection of an effect of the active treatment in any of the individual studies.

If there has been a recent rapidly unstable mood or mixed state, this may be a particular reason to consider lamotrigine. Lamotrigine is not commonly a single first-line agent in bipolar-I disorder because of its limited effect on the risk of manic relapse. Monotherapy is more feasible in bipolar-II disorder given its efficacy in bipolar depression (I, Geddes, *et al.*, 2009) and evidence for benefit in rapid cycling bipolar-II patients (Bowden, *et al.*, 1999). There are also safety concerns with lamotrigine because of the risk of serious rashes that occasionally proceed to Stevens–Johnson syndrome. Patients must be aware that a rash must prompt immediate consultation and potentially drug discontinuation.

Electro-convulsive therapy

ECT is also effective in severe depression: the relevant trials will have included bipolar cases, although trials exclusively in bipolar disorder do not exist (I, The UK ECT Review Group, 2003). A comparison of outcomes in refractory depressed patients with unipolar or bipolar illness courses showed limited but equivalent efficacy (Grunhaus, *et al.*, 2002).

Beliefs about ECT in the general population appear to remain influenced by unfavourable media portrayal (Lebensohn, 1999) and this has not diminished. Clinicians have a responsibility to try and combat ignorance and prejudice, it may be helpful to allay fears that ECT is often used against the will of individual patients (S).

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

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. Of course, clinically there is an obvious gradient between those patients showing highly variable mood and those with a much more episodic pattern. There have been few efforts to differentiate the treatment responses along this gradient, except by reference to 'rapid cycling' which is an imprecise course specifier.

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 specifically) (Gijsman, *et al.*, 2004).

Venlafaxine (and duloxetine) may have a similarly increased risk of switching, perhaps due to action on serotonin and nor-adrenaline reuptake. In the Stanley network study, patients treated with venlafaxine switched to mood elevation (defined as a YMRS (Young Mania Rating Scale) rating over 13) in 31% of case, compared with sertraline (15%) and bupropion (14%); response rates were similar around 50%, but there was no placebo control (Post, *et al.*, 2006). These rates are high, which seems likely to have been due to the inclusion of rapid cycling patients.

The Munich audit data and clinical common sense suggest that an antimanic in combination with the antidepressant may reduce the risk of a manic switch in depressed patients with a high risk of mania. The antimanic agent could be valproate, lithium or an antipsychotic. Fluoxetine plus olanzapine is effective in reducing depressive symptoms without provoking manic relapse (Tohen, *et al.*, 2003). This again appears to support the general recommendation to combine an effective antidepressant with an antimanic 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). This is echoed more dogmatically in recent NICE guidance. Of course, the absence of evidence is not evidence of the absence of, in this case, long term benefit (see also below).

Discontinuation of an antidepressant should follow recommendations in related BAP guidelines and taper over 4 weeks if possible (Anderson, *et al.*, 2008). In particular, the possibility of adverse withdrawal effects should be discussed and reassurance offered.

Paradoxical manic episodes have been described during acute withdrawal of antidepressants (Goldstein, *et al.*, 1999). Since both the antimanic and the antidepressant medicines should be terminated together if the intention is that treatment should be simply for an acute episode, it appears logical to stop the antidepressant first, rather than both at once.

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

3. 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.
- The number of evidence-based options for long-term treatment has increased. There is accordingly, a more complicated choice facing both doctors and patients in prescribing both mono- and combination therapy.
- Lithium prevents relapse of mania but is relatively less effective against depression (I). The highest dose that produces minimal side effects should be employed. Levels less than 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).
- A wide range of other medicines such as anticonvulsants (CBZ, lamotrigine, valproate) and antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) have been studied as monotherapy or in combination with lithium or valproate and shown to reduce the risk of relapse to mania or depression. Average effects for mania vis-à-vis depression vary but offer a limited guide to individual treatment choice.
- Lamotrigine is more effective against depression than mania in long-term treatment (I) and should be considered where depression is the major burden of the illness and the risk of manic relapse is low (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 antimanic efficacy (C).
- Discontinuation of long-term treatment is not indicated when there is 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 (I). Poor adherence is a contraindication to lithium because of risk of new illness episodes on discontinuation (I).

Key uncertainties

- There is uncertainty in relation to the effects of long-term treatment on day-to-day or week-to-week mood stability.
- Successful long-term management, judged by syndromal relapse prevention, 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.
- The effectiveness of using drugs such as antipsychotics intermittently to treat early warning signs and avert full blown episodes, while supported by clinical opinion is not underpinned by controlled evidence.
- Long-term complications of medicines used to treat bipolar disorder are currently extrapolated from relatively short-term observations. Longer term safety is less well established.

Mood stabilisation 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. 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 get an appointment with their psychiatrist.

Recent studies have prompted a reevaluation 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. While lithium clearly has properties in that direction and in individual cases may be seen to be effective in both senses, it is on average more effective against the manic pole of the illness. In the case of lamotrigine the effects are in the opposite direction. Quetiapine appears to have equal efficacy. Thus, the magnitude of relevant efficacy against recurrent mania and depression for the medicines used long term in bipolar disorder is quite variable. The terminology for 'mood stabilizers' has been reworked, but there is not yet a clear consensus whether it will be useful (Ketter and Calabrese, 2002).

We remain significantly uncertain as to the extent that many medicines used for long-term treatment in bipolar disorder actually do 'stabilize' mood. These have included the anticonvulsants valproate, CBZ, 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. Specifically for gabapentin and topiramate, controlled studies in acute mania were negative (gabapentin I, Pande, *et al.*, 2000; topiramate I, Kushner, *et al.*, 2006). There remains some interest in using topiramate for weight reduction in obese bipolar patients (Chengappa, *et al.*, 2006).

Long-term treatment with lithium and anticonvulsants

There have been adequate numbers of patients randomised into placebo-controlled long term or 'maintenance' trials of lithium

treatment dating from soon after its introduction (I, Burgess, *et al.*, 2001) and more recently when lithium has been a reference compound for other treatments (Geddes, *et al.*, 2004). Relapse rates on lithium over a year or so were 40% compared with about 60% on placebo. That means, in general, one would need to treat about four patients for a year with lithium to avoid one relapse. There are fewer relapses at times beyond a year: the patients who do well on Lithium continue to do well on it. Recent naturalistic comparison of patients who discontinue lithium slowly and those who did not after 2 years of mood stability has confirmed the advantages of lithium in a real world sample (Biel, *et al.*, 2007). Relapse was three times higher in the patients who continued. Median survival time to illness recurrence for patients continued on lithium was 7.33 years (95% confidence interval (CI) 5.67–9.67); that for patients discontinued from lithium was 1.33 years (95% CI 0.33–2.33). The increased risk of relapse after slow lithium discontinuation is also seen in good responders to lithium after 5 years mood stability (Yazici, *et al.*, 2004).

Manic relapses are 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 relapses compared with 23% for depressive relapses for lithium. In fact, lithium is only marginally effective on current evidence at protecting against depressive relapses.

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

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

Two lamotrigine maintenance trials individually support an effect against depression, not mania (I, Goodwin, *et al.*, 2004). The samples were enriched for lamotrigine tolerance and compared lamotrigine, lithium and placebo. In one, the index episode was mania and, in the other, depression. The results from both trials are mutually supportive in showing an advantage for lamotrigine in the prophylaxis of depression. There was a comparable advantage to lithium for mania. There was neither excess of depressive episodes in lithium-treated patients nor manic episodes in lamotrigine-treated patients compared with 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.

The strongest evidence amongst those medicines frequently referred to as mood stabilisers for bipolar-I disorder is still for lithium. Lithium certainly prevents manic and probably depressive relapses.

Long-term treatment with antipsychotics

Antipsychotics have often been 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 one randomised, placebo-controlled study of a classical antipsychotic in relapse prevention did not find efficacy and reported some worsening of depressive symptoms (II, Esparon, *et al.*, 1986), but it was inadequately powered. A small study of perphenazine suggested that its continuation increased the risk of depression (Zarate and Tohen, 2004), the first controlled evidence for an effect frequently attributed to the classical antipsychotics. 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 (II, White, *et al.*, 1993; Littlejohn, *et al.*, 1994).

A number of studies of newer antipsychotics have now been completed employing what is usually called a relapse prevention design. Patients enter such studies from an acute episode, usually of mania, in which the medicine of interest is used as a primary treatment. This enriches the sample for both efficacy and tolerability. However, it bears on clinical practice, where after an acute response the question is whether or not to continue in the long term.

Olanzapine has been shown to be effective in a placebo-controlled relapse prevention study. The excess of early relapse in this study suggests a contribution from withdrawal effects to the apparent effect size (Tohen, *et al.*, 2006). Olanzapine was also slightly superior to lithium as monotherapy after acute response to the combination of lithium with olanzapine but produced significant excess weight gain (Zarate and Tohen, 2004; Tohen, *et al.*, 2005). This study shows that olanzapine prevents early manic relapse after lithium withdrawal, a useful practice point.

Quetiapine has been shown to be highly effective as monotherapy in the prevention of relapse *to* either pole of the illness, for patients entering treatment *from* either pole of the illness: data are currently available only in published abstracts (Vieta, *et al.*, 2008a).

The data for other atypicals also appears to be compatible with relapse prevention. Aripiprazole was more effective than placebo after acute and continuation treatment of mania with aripiprazole: no effect on depression was discernible. Acute withdrawal of the active agent did not produce an excess of early relapse in this study (Keck, *et al.*, 2007).

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, e.g. 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 (II, Suppes, *et al.*, 1999). Rapid cycling remains a major clinical challenge. Secondary analysis of the acute depression studies with quetiapine suggest efficacy

in the short term for rapid cyclers (Vieta, *et al.*, 2007), but the real issue is long-term stability. A small pilot study of vagal nerve stimulation is also compatible with some benefit in resistant rapid cycling patients, a very disabled group (Marangell, *et al.*, 2008).

Risperidone is available as a depot formulation and may be useful in poorly compliant bipolar patients at high risk of manic relapse (Malempati, *et al.*, 2008; Vieta, *et al.*, 2008b).

Long-term treatment with antidepressants

Whether or not antidepressants should be used long term in bipolar disorder remains uncertain. One small maintenance study (II, Prien, *et al.*, 1984) has had an important influence in this area since 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 has been 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 very strong (I, Geddes, *et al.*, 2003) but of uncertain applicability to bipolar disorder. The equivalent evidence from bipolar patient samples is almost completely absent. There is nonrandom evidence for successful long-term prophylaxis with antidepressants in bipolar patients also receiving combination treatments such as lithium, valproate, CBZ and antipsychotics (II, Altshuler, *et al.*, 2001). These findings are far from compelling either way. Expert North American opinion has long sought to discourage the use of antidepressants in bipolar disorder (Ghaemi, *et al.*, 2001; Ghaemi, *et al.*, 2003). Clinicians will have to use clinical judgement in deciding whether an individual patient should continue with an antidepressant. There is not sufficient evidence to recommend discontinuation (as in recent NICE guidance) since this goes beyond the evidence.

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.

Bipolar-II patients and, in particular, patients with bipolar spectrum depression have not been sufficiently investigated except in the quetiapine studies. Anecdotally, it is possible that effective treatment with antidepressants is possible without an additional antimanic (Parker, *et al.*, 2006). 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, as yet, little more than anecdote to suggest that, long term, combination treatment is actually superior to monotherapy. The systematic study of combinations of the currently available medicines appears highly desirable. Effective prevention of disease progression may require combination treatment from as early in the illness course as possible. At present we are uncertain as to what combination if any to recommend from a first episode. It is to resolve such key uncertainties that there is widespread support for large simple trials in bipolar disorder: such studies require the creation of adequate capacity in the form of collaborative networks of clinicians who can agree to collect data in a compatible format and incorporate simple trial methodology into everyday clinical practice (Geddes and Goodwin, 2001). Systematic audit of naturalistic databases could provide important complementary evidence.

Suicide

Suicide is a major long-term risk for patients with bipolar disorder. For patients identified by admission to hospital, rates are about 0.4%/year (Tondo, *et al.*, 2003). This is 20-fold greater than population rates and translates into risks at long-term follow-up between 3%–6% (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. The risk of suicide is highest early in the course of the illness (Hoyer, *et al.*, 2000). Suicide is associated with male gender, attempted suicide, hopelessness at index admission and, perhaps, a family history. It is not clearly associated with the use of drugs and alcohol, a bipolar-I as opposed to bipolar-II diagnosis or mixed states (Hawton, *et al.*, 2005).

The lifetime prevalence of nonfatal suicidal behaviour (attempted suicide or self-harm) in those with bipolar disorder is approximately 30% (Chen and Dilsaver, 1996; Tondo, *et al.*, 2003) and may be as high as 50% in secondary care samples (Valtonen, *et al.*, 2005). Studies have shown that a wider range of factors are associated with attempted suicide than suicide itself, possibly because the former is a more common outcome. These factors include being single, a positive family history of suicide, mixed states, rapid cycling, alcohol and substance misuse, comorbid anxiety and, possibly, early abuse or a bipolar-II diagnosis (Hawton, *et al.*, 2005). Aggression and impulsivity may also be associated with suicide attempts (Oquendo, *et al.*, 2000; Oquendo, *et al.*, 2004).

Thus, the risk of suicidal behaviour (both fatal and nonfatal) is substantially higher in patients with bipolar disorder than in the general population, and this risk is high early in the course of illness, and during depressive phases.

An equally important perspective, however, is the potential for successful long-term treatment to reduce suicide risks 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 largely 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 (I, Tondo, *et al.*, 2001). One long-term RCT also found suicides and attempted suicides to be associated with CBZ and not lithium treatment (II, Thies-Flechtner, *et al.*, 1996). Indeed, a meta-analysis of all the randomized-controlled data for lithium suggests an effect on suicide which appears to be consistent across many studies, most of which are individually inconclusive because of inadequate power (I, Cipriani, *et al.*, 2005).

The National Confidential Inquiry data for deaths of psychiatric patients in England and Wales (1997–2006) included 1243 bipolar patients (10% of the sample) (N. Kapur, personal communication). Only 390 (31%) were compliant with mood stabilisers at time of death. This is an important measure of how ineffective management strategies currently are for our patients. Only 13 (about 3% of all those prescribed mood stabilisers) died by poisoning with these drugs, so the benefit/risk potential appears acceptable. The challenge appears to be the delivery of effective treatment.

In recent years, there has been a considerable, perhaps excessive emphasis on risk assessment in UK Mental health policy. Risk assessment implicitly or explicitly assumes that it is possible to identify those at high risk and prevent adverse events like suicide by means of a targeted prevention strategy. This is a fallacy when event rates are low and risk factors are only weakly predictive of the event, as is the case for suicide. In fact, the majority of suicides will occur in patients who are, on the basis of risk assessment, classified as relatively low risk (Powell, *et al.*, 2000). It is probably a better strategy to recognise that all bipolar patients, especially those who have been admitted to hospital and are prone to depression, are at risk of suicide. The most logical approach is then to provide superior long-term clinical care to as many of them as possible.

Adverse effects of long-term treatment

Physical health among patients with bipolar disorder is poor compared with population controls. They represent a high risk group who merit much greater efforts than hitherto to both detect and prevent physical health problems particularly related to obesity, lack of exercise and smoking. Unfortunately, a disappointing number of the treatments used long term in bipolar disorder may exacerbate these risks.

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 to moderate calorie intake.

Although, this has traditionally been a cosmetic concern, strongly felt by patients, it has an important medical corollary. To understand the current scale of the problem, a cross-sectional study ($n = 4310$; mean age 53 years) found that 17% of patients with bipolar disorder had type 2 diabetes and 35% had hypertension (Kilbourne, *et al.*, 2004). In a separate study, one-third of bipolar patients died of circulatory causes (Rege-nold, *et al.*, 2002). These figures are two to three times higher than population rates.

Effective medical management of physical illness in patients with severe bipolar disorder is a major challenge. The so-called metabolic syndrome, a composite of biochemical, blood pressure and weight indices is associated with older age, higher body mass index and higher values for each individual criterion of the metabolic syndrome but *not with specific diagnoses or exclusively with antipsychotic treatment regimens*. The absolute waist circumference (>102 cm (40 in.) in men and >88 cm (35 in.) in women) and the waist-hip ratio (>0.9 for men and >0.85 for women) are both used as measures of central obesity. In a small study, the presence of central obesity was the most sensitive indicator (92.0%) and fasting glucose 7.0 mmol/l or over was most specific (95.2%) in correctly identifying the presence of metabolic syndrome (Straker, *et al.*, 2005). Thus, we know what is required for identifying the problem, but optimal interventions that work in the long term are a challenge. Small short-term controlled studies suggest that antipsychotic induced weight gain can be attenuated by behavioural intervention, and larger scale implementation produces improvements in some measures of physical health (Álvarez-Jiménez, *et al.*, 2006; Smith, *et al.*, 2007c). However, it is a disappointingly consistent finding that, among obese patients, the weight lost as a result of the most widely available treatments for obesity is almost always regained (Byrne, *et al.*, 2004).

In this country, a retrospective cohort study using the GP Research Database compared 46,136 patients with 'severe mental illness' (SMI) with 300,426 without SMI. Hazard ratios (HRs) for coronary heart disease (CHD) mortality in people with SMI compared with controls were 3.22 (95% confidence interval [CI], 1.99–5.21) for people 18–49-years old and 1.86 (95% CI, 1.63–2.12) for those 50–75-years old. For stroke deaths, the respective HRs were 2.53 (95% CI, 0.99–6.47) and 1.89 (95% CI, 1.50–2.38). Event rates in these age groups are quite low, but increased HRs for CHD mortality occurred irrespective of sex, SMI diagnosis or prescription of antipsychotic medication during follow-up. However, a higher prescribed dose of antipsychotic predicted a slightly greater risk of mortality from CHD and stroke (Osborn, *et al.*, 2007).

Several antipsychotics, including clozapine, olanzapine and, to a lesser extent, quetiapine are particularly associated with increased weight gain and the risk of dyslipidaemia, hypercholesterolaemia and elevated glucose (Meyer and Koro, 2004; Lieberman, *et al.*, 2005; Meyer, *et al.*, 2008). In an increasingly obese population, this is a growing concern. The current challenge is to understand the relative future contributions of the drugs themselves and that associated with SMI *per se* in the long term. Thus, bipolar patients appear to be at risk of more

medical comorbidity of all sorts than the general population. Whether this is due primarily to genetic or lifestyle factors, is not yet understood. However, there is no doubt that antipsychotics in particular have the potential to make the situation worse and must be used cautiously (Newcomer, 2007).

Cigarette smoking is more common in psychiatric patients generally. Heavy smoking and obesity account for most of the excess mortality of patient populations with SMI (Compton, *et al.*, 2006). There is also evidence for genetically based tendency for patients to smoke which, to some extent, overlaps with risks for major mental illness (Leonard, *et al.*, 2001). There is largely untapped scope for efforts at smoking cessation in bipolar patients.

Prolactin (PRL) elevation may lead to secondary hypogonadism and low bone mineral density (BMD), the most potent risk factor for osteoporotic fractures. Lifetime risk of such fractures for women in the general population is already substantial. Decreased BMD and increased fracture risk have been shown in SMI patients (Meyer and Koro, 2004; Lehman and Meyer, 2005; Howard, *et al.*, 2007). PRL and gonadal function are hardly ever assessed in women on antipsychotics, BMD is not measured, and osteoporosis remains undiagnosed, let alone prevented or treated. Hyperprolactinaemia can occur with many antipsychotics, although, among the atypical agents, the risk is highest with risperidone and amisulpride (Haddad and Wieck, 2004). All premenopausal women on the typical antipsychotics, amisulpride and most on risperidone (including at low doses) are at risk of amenorrhoea, low or undetectable oestradiol levels and many will also have low BMD. Hence, prevention and treatment of osteoporosis must become a target for improvement in physical health of potentially neglected populations of patients.

In young patients, hyperprolactinaemia may retard or prevent puberty and the use of PRL-sparing medicines has been recommended for patients under the age of 25 years (Javaid and Cooper, 2002).

TD remains a concern for patients treated long term with antipsychotics (Keck, *et al.*, 2000). Acute EPS are still regarded as a predictor of subsequent TD, so the lower EPS associated with the use of the atypical antipsychotics and the use of the typical drugs at lower doses should reduce the long-term risk. Current data on TD with atypical antipsychotics is supportive if not conclusive of reduced risks with the atypical agents (Correll, *et al.*, 2004).

There is a general problem that the long-term complications of medicines used to treat bipolar disorder are currently extrapolated from relatively short-term intervals of controlled observation. Longer term safety is less well established for any of the medicines we currently recommend to our patients.

Specific psychological interventions in bipolar disorder

- The key components of successful psychological treatment for bipolar disorder appear to include: (II)
 - o Knowledge and 'psycho-education' with improved evaluation of personal risks posed by the illness

- o Self monitoring
- o Self regulation: action plans and modification of behaviours
- o Increased adherence to medicines

Key uncertainties

- The optimal packages that can be beneficially introduced during acute depressive or hypomanic episodes and for maintenance.

Cognitive behaviour therapy

Although, 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 (review by Scott, 1996). A preliminary trial in 42 subjects suggested that CBT could speed-up 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 produced important reductions in rates of syndromal relapse, depression symptom reduction, less mania symptom fluctuation and higher social functioning over a 1-year period compared to treatment as usual (Lam, *et al.*, 2003). In a 2-year follow-up paper, the longer term effects were found mainly on depression (Lam, *et al.*, 2005b). The study targeted patients who were prescribed mood stabilisers and were still suffering from frequent relapses. Compared to treatment as usual, such enhancement of clinical care appeared to be helpful. Treatment included 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. Disappointingly, the findings from the Lam study were not replicated in a larger and more pragmatic CBT study, which showed no benefit at all for a large sample of patients versus treatment as usual (Scott, *et al.*, 2006).

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 proportionally benefit from the more intensive approaches more than less challenged patients for whom a lighter touch may be sufficient. However, this was not the finding in the multicentre UK CBT study (Scott, *et al.*, 2006), which found that CBT was more effective than treatment as usual for patients with fewer than 12 prior episodes. This finding remains controversial (Lam, 2006).

Interpersonal and social rhythm therapy

Interpersonal and social rhythm therapy (IPSRT), a descendent of the interpersonal psychotherapy of depression, consists of

interpersonal problem-solving, clarification, and interpretation to help patients resolve issues related to grief, role transitions, role disputes, or interpersonal deficits. IPSRT emphasizes the role of social and circadian rhythm dysregulation in the onset of manic episodes. Unlike CBT, IPSRT has been tested primarily with bipolar patients who began treatment shortly after an acute episode of mania or depression. In the Pittsburgh maintenance therapies for bipolar disorder trial (Frank, *et al.*, 2005), 175 patients were randomly assigned during an acute treatment phase to weekly IPSRT plus pharmacotherapy or active clinical management plus pharmacotherapy. Once patients had recovered by research criteria, they were re-randomized at the beginning of a maintenance phase to IPSRT or active clinical management on a monthly basis for up to 2 years. IPSRT in the acute phase was associated with longer survival time prior to recurrences in the maintenance phase than clinical management. However, continued treatment with IPSRT during the maintenance phase did not affect recurrence rates during maintenance treatment.

Family-focused therapy

FFT is a 9-month, 21-session outpatient treatment for patients and their immediate family members (spouse, parents, siblings). It consists of psychoeducation about bipolar disorder, communication enhancement training, and problem-solving skills training. Given in conjunction with pharmacotherapy during the post-episode period, FFT aims to hasten stabilization and reduce the likelihood of early recurrences. FFT has been tested in one open trial with an historical comparison group ($N = 32$; Miklowitz and Goldstein, 1990), two randomized trials focusing on relapse prevention (Miklowitz, *et al.*, 2003; Rea, *et al.*, 2003); one randomized trial involving stabilization of bipolar depressive episodes (Miklowitz, *et al.*, 2007), and one randomized trial involving adolescents with the disorder (Miklowitz, *et al.*, 2008). Overall, FFT is associated with a 35%–40% reduction in recurrence rates over 2 years, and a 48% increase in recovery rates over 1 year. Its effects appear to be stronger in stabilizing depressive episodes than in stabilizing manic episodes. FFT also appears to enhance adherence with lithium and/or anticonvulsant regimens (Miklowitz, *et al.*, 2003).

Group treatments

Group psychoeducation appears to be a highly effective adjunct to pharmacotherapy in relapse prevention. Colom and associates (Colom, *et al.*, 2003) randomly assigned recovered bipolar patients to a 21-session structured psychoeducation group or an unstructured support group, both with standard pharmacotherapy. Results at the end of 2 years indicated a lower relapse rate in group psychoeducation (67%) than in the unstructured group (92%). Patients in group psychoeducation also had fewer (and shorter) hospitalizations, and maintained higher and more stable lithium levels. Benefits in the study group were preserved at 5 years (Colom, *et al.*, 2009). Psychoeducation is an umbrella term that includes components of illness awareness, treatment adherence, early detection of prodromal symptoms and recurrences and lifestyle regularity.

Two large-scale randomized trials have examined the effectiveness of group psychoeducation within the context of multi-component care management plans. Bauer and colleagues (Bauer, *et al.*, 2006a; Bauer, *et al.*, 2006b) examined a 'collaborative care' (CC) program for bipolar patients at 11 Veterans' Administration sites. The intervention included enhanced access to psychiatric care through a nurse coordinator; medication practice guidelines for the psychopharmacologist; and a group psychoeducational treatment to improve patients' self-management skills. Over a 3-year period, patients in the CC treatment spent fewer weeks in manic episodes than patients who received continued VA care ($N = 306$). Improvements in the CC group were also observed in social role function, mental quality of life, and treatment satisfaction, especially in the second and third treatment years.

In the largest randomized trial to date of a psychosocial treatment for bipolar disorder ($N = 441$) (Simon, *et al.*, 2005; Simon, *et al.*, 2006), a 2-year multicomponent care-management intervention was compared to treatment-as-usual among patients in a health care network. Over 2 years, patients in the multicomponent program had significantly lower mania scores and spent less time in manic or hypomanic episodes than those in the comparison group. There were no effects on depressive symptoms. Interestingly, the program only had effects among patients who had clinically significant symptoms upon entering the program. So, it may be best to target patients who do not achieve full remission for this kind of multicomponent intervention. Indeed, mood disorder patients who do not achieve full remission with pharmacotherapy are highly recurrence-prone (Rush, 2006; Perlis, *et al.*, 2006). Overall, group psychoeducation appears to be a viable and possibly cost-effective alternative to individual or family approaches in the stabilization of manic, and in one study depressive symptoms.

Comparison of psychosocial approaches: the STEP-BD study

The STEP-BD examined pharmacologic and psychosocial interventions in a practical clinical trial across 22 US treatment centers (Sachs, *et al.*, 2007). In one part of the program, 293 bipolar-I and bipolar-II patients from 15 sites were randomly assigned to one of three intensive psychosocial treatments (30 sessions over 9 months of FFT, IPSRT or CBT) in conjunction with best practice medication treatment or a control treatment called CC. The CC involved three psychotherapy sessions over 6 weeks and focused on developing a relapse prevention plan. All patients were in an acute episode of bipolar depression at the time of treatment randomization. Over 1 year, being in any of the intensive psychotherapies was associated with a higher recovery rate from depression than being in CC (Miklowitz, *et al.*, 2007). On average, patients in intensive treatment recovered within 169 days, as compared to 279 days in the CC condition. Patients in intensive treatment were also 1.6 times more likely to be clinically well in any given month of the study than patients in CC. The STEP-BD program suggests that psychotherapy is a vital part of the effort to stabilize episodes of depression in bipolar illness, and that acutely depressed

patients may require more intensive psychotherapy than is typically offered in community mental health centres.

Further work is required to determine whether there are real differences between therapies and whether simpler interventions are worthwhile. The provision of greatly increased levels of psychotherapy to vulnerable patients is not without its risks (Nutt and Sharpe, 2008).

4. 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). Although the selection of new treatments with fewer side effects seems reasonable, older treatments that worked previously may on occasion be the better choice in view of the imperative to achieve response.

Substance abuse

Group psychoeducation has been examined in patients with comorbid substance abuse disorders, who are highly relapse-prone (Weiss, *et al.*, 2007). A total of 62 patients with bipolar disorder and substance or alcohol dependence received 20 weeks of 'integrated group therapy' or group drug counseling. The integrated group used a CBT model focused on the similarities between bipolar and substance dependence disorder in cognitions and behaviors during the recovery and relapse periods. The group drug counseling focused exclusively on encouraging abstinence and acquiring coping skills to address substance craving. Over an 8-month period of treatment and follow-up, patients in the integrated groups had half as many days of substance use as patients receiving only drug counseling. The results were only significant for days of alcohol use, not drug use. No differences were observed in relapses of bipolar disorder; in fact, patients in the integrated groups had higher depression and mania scores during treatment and follow-up than patients in drug counseling. The authors concluded that the dual diagnosis focus of the groups increased the likelihood that patients would recognize and report mood disorder symptoms. The possibility that decreasing alcohol abuse 'unmasks' subsyndromal mood disorder symptoms, deserves further study.

Bipolar disorder and pregnancy

Effect of medication on fertility Bipolar patients may wish to get pregnant. Some psychotropic medicines may reduce fertility. Thus, an increased incidence of polycystic ovarian syndrome (Joffe, 2007), putatively associated with valproate use may reduce fertility but be reversible on stopping medication. Some antipsychotics may impair ovulation by causing hyperprolactinaemia and disruption of hypothalamic–gonadal axis. Conversely, switching to a PRL-sparing antipsychotic may cause return of fertility and unplanned pregnancy. CBZ reduces the effectiveness of oral contraceptives (OC) by enzyme induction.

Women of childbearing potential As a considerable proportion of pregnancies are unplanned, consideration of possible current and future pregnancy must be given when managing all women of reproductive potential. Most of the danger for organ development is in the first few months, possibly even before a woman is aware that she is pregnant. Consequently all female patients of childbearing age should be advised about the importance of effective contraception (II, Smith and Whitfield, 1995).

Increased risk in relationship to childbirth Suicide is a major cause of maternal death in developed countries (Oates, 2003).

Childbirth increases the risk of relapse in patients with bipolar disorder in the postpartum period. In fact, this effect is most striking with first babies and for first psychiatric admissions (I, Terp and Mortensen, 1998). Women are at a 23-fold increased risk of admission with a bipolar episode in the first postpartum month (Munk-Olsen, *et al.*, 2006). Women with a history of bipolar disorder have at least a 25% risk of suffering a severe recurrence following delivery (Jones and Craddock, 2001). Bipolar women with a previous history of a severe postpartum episode (puerperal psychosis) and bipolar women with a family history of puerperal psychosis are at particularly high risk with greater than one in two deliveries affected (Jones and Craddock, 2001; Robertson, *et al.*, 2005). All decisions about management must, therefore, be made with a clear recognition of the very high risk of recurrence for bipolar disorder in relationship to pregnancy and childbirth.

Identifying women at high risk of relapse The high risk to pregnant women with a history of bipolar disorder must be recognised by psychiatric and antenatal services. The increased risk should be communicated to all healthcare professionals involved in the pregnancy and postpartum care. All women at antenatal booking should be asked about a history of bipolar disorder. Pregnant women with a history of bipolar disorder should be under the care of psychiatric services.

Making decisions about medication The potential benefits of adherence 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. The doses of medi-

cines required to control symptoms may be higher if, for example, a manic episode occurs. Against the benefits there are some risks. These include teratogenesis, neonatal side effects that may reflect drug toxicity and withdrawal effects.

Ideally, pregnancy should be planned in consultation with the psychiatrist and include a full explanation of the treatment options and their risks and benefits. Input from specialist perinatal or affective disorder services either preconception or in early pregnancy should be considered when available. Treatment options include continuing the existing medication throughout pregnancy, switching to alternative medicines associated with lower foetal risk prior to conception, withdrawing some or all medication prior to conception and reintroducing it either after the first trimester or immediately after birth. Management decisions must be the result of an individualised assessment and consideration of the balance of risks and benefits. The chosen option will depend on the patient's past history, the particular medications prescribed and the patient and clinician's attitudes to risk and personal preferences.

Risks of discontinuation of medication There is a high risk of relapse in affective disorder if medication is discontinued. Thus, 52% of women who discontinued lithium during pregnancy relapsed, and 70% of the women who remained stable after lithium discontinuation relapsed during pregnancy in the postpartum period (Viguera, *et al.*, 2000; Meyer and Koro, 2004). In a recent prospective observational clinical cohort study of 89 pregnant women with DSM-IV bipolar disorder, overall risk of at least one recurrence in pregnancy was 71%. Those who discontinued (versus continued) mood stabilizer treatment, were twice as likely to relapse and the median time to relapse was much sooner. Rapid discontinuation was associated with higher risks of relapse. Most relapses were depressive or mixed (74%), and 47% occurred during the first trimester (Viguera, *et al.*, 2007). Treatment may involve exposure to higher doses of psychotropic medicines than would be implied by long term maintenance treatment. Maternal depression has a negative impact on child development (Rice, *et al.*, 2007).

Risks of taking medication in pregnancy The potential benefits of adherence with long-term treatment during pregnancy for a woman with bipolar affective disorder are a reduced risk of relapse or recurrence, a higher chance of remaining free of symptoms and consequently less interference in the developing relationship with her child. Weighed against the benefits are a number of risks. These include teratogenesis, neonatal side effects that may reflect drug toxicity or withdrawal and long-term effects on development.

The risk of major congenital malformations in the general population is surprisingly high at 2%–4% and increases with maternal age. Consideration of the teratogenic potential of medication must be made against this background risk. The evidence base with regard to reproductive safety is constantly changing and due to the modest sample sizes of most studies, a precise estimate of risk is not possible: very wide confidence

intervals are typical. More data exists for the antiepileptic drugs because of their use in epilepsy.

Sodium valproate and CBZ Malformation rates are increased two- to threefold in valproate-exposed babies with rates in the range of 6%–11% reported (II, Kaneko, *et al.*, 1999). CBZ exposure has been found to be associated with a twofold increased malformation rate in most studies (II, Rosa, 1991). Valproate and CBZ are associated with a range of congenital abnormalities including severe neural tube defects (NTD) and importantly valproate use has been associated with developmental delay with a reduced IQ in exposed children (Adab, *et al.*, 2004). The risk of congenital abnormalities is dose related with valproate (blood levels over 70 µg/ml and doses of 1000 mg daily or higher implicated) and increases with the number of antiepileptic agents prescribed (II, Samren, *et al.*, 1999).

Lithium Lithium register studies in the 1970s suggested a 'specific association' with Epstein's anomaly believed to represent a many hundredfold increased risk of this rare but serious malformation. Subsequent prospective cohort studies not subject to the same biases have found the risk to be considerably lower. Only two such studies have been reported with a total of only 165 exposures but total malformation rates were increased 1.5-fold (3%) in the larger study (Jacobson, *et al.*, 1992) and 3-fold (12%) in the smaller (Källén and Tandberg, 1983).

Typical and atypical antipsychotics Although there are some reports of malformations born to babies exposed to typical antipsychotics there is no consistent evidence of teratogenic risk (Altshuler *et al.*, 1996). There is more limited data available on the newer atypical antipsychotics and therefore safety in pregnancy remains unknown. However, the data that is available does not indicate a specific teratogenic risk in humans (McKenna, *et al.*, 2005; Reis and Kallen, 2008).

Therefore, although many medications used in the treatment of bipolar disorder are associated with an increased risk, the great majority of women who conceive while taking them will deliver a normal baby. The impact of a baby born with a severe malformation, however, must be factored into the risk benefit analysis. The current available data suggests that there are particular concerns with the use of valproate, including long-term effects on cognitive development. It is, therefore, appropriate that all other therapeutic options are pursued in women taking valproate who wish to become pregnant and that the use of valproate is not considered a first-line option in women of reproductive potential.

Antidepressants Teratogenic effects have not been reported with tricyclic antidepressants (Simon, *et al.*, 2002). No increased risk of major malformations compared to the general population was seen in a meta-analysis of seven prospective cohort studies of first trimester exposure to newer antidepressants (Einarson and Einarson, 2005). However a more recent cohort study reported an increase malformation risk with SSRIs (Wogelius, *et al.*, 2006). Another study reported

that first trimester exposure to paroxetine, but not other SSRIs, was associated with an increased risk of cardiac defects (Kallen and Olausson, 2007). The teratogenic potential of tricyclic antidepressants has been less studied than for the SSRIs and they cannot be assumed to be safer alternatives.

Managing women on medication in pregnancy Women who have taken potentially teratogenic drugs during the first trimester should be advised about prenatal diagnosis and offered maternal alpha foetoprotein screening to detect NTDs and a high resolution ultrasound scan at 16- to 18-week gestation. High-dose folate supplementation (4 or 5 mg) is advised for pregnant women taking CBZ and valproate. There have been reports of women who took valproate and high doses of folic acid during pregnancy but gave birth to children with NTDs (Duncan, *et al.*, 2001), so it is unclear whether folate offers no or only partial protection against the increased risk of NTD associated with antiepileptic use. For some medications during pregnancy, prescribing slow-release formulations or more frequent dosing regimes can minimize high peak levels.

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 and lithium levels must be monitored closely in pregnancy and particularly through labour and in the immediate postpartum.

Neonatal effects of maternal psychotropic medication If patients are taking medicines up to childbirth, both toxic effects and withdrawal effects have been described for many psychotropic medications though proving causality is often difficult (Ebbesen, *et al.*, 2000). Vigilance in caring for babies of mothers taking psychotropic agents is recommended. Benzodiazepines may depress neonatal respiration or cause drowsiness, hypotonia or withdrawal symptoms. Antipsychotics have been reported to cause EPS. Tricyclics have been reported to cause urinary retention and functional bowel obstruction. Lithium has been associated with thyroid goitre, hypotonia and cyanosis. CBZ has caused neonatal bleeding and is an indication for prophylactic vitamin K.

In the case of antidepressants, which are prescribed in as many as 6.5% of women delivering babies, revised classlabelling has emphasized an increased risk of jitteriness, poor feeding, crying and seizures. The mechanisms are likely to be attributable to toxicity, withdrawal or a combination of factors (Haddad, *et al.*, 2005). Discontinuation in pregnancy or a switch to fluoxetine (the long half-life may reduce withdrawal effects) are management options (Anderson, *et al.*, 2008). The potential impact of withdrawal of psychiatric drugs on the mothers' mental state needs to be considered when making treatment decisions.

Although there is little systematically collected evidence, ECT is generally considered to be safe to administer to pregnant women.

Breastfeeding Breastfeeding requires an understanding by patients of the potential risks of toxicity to the neonate and the need for vigilance in their care. All psychotropic drugs enter breast milk but the ratio between infant and maternal plasma levels varies greatly. The rates of adverse effects are uncertain, but there are sporadic reports of problems with, for example, toxicity due to lithium, hepatic dysfunction due to CBZ and thrombocytopaenia or anaemia attributed to valproate. Factors in the baby are also important with a greater risk in babies who are premature or with systemic illness. In general, the risks to the infant are the same as those for any patient exposed to the medicine, so clozapine is usually regarded as contraindicated because of the risk of agranulocytosis. Lamotrigine will carry the possibility of rash. These risks need to be balanced against the benefits of breastfeeding (I, Austin and Mitchell, 1998). All breastfeeding women on medication should be advised about the need for vigilance for side effects in the baby.

Antidepressants are usually present in breast milk in low concentration but there is large individual variation and some infants have developed plasma levels higher than maternal plasma levels. Abrupt withdrawal of sertraline may have caused neonatal withdrawal effects and similar effects might be expected for other SSRIs with relatively short half-lives.

Due to its narrow therapeutic index lithium is generally regarded as being a relative contraindication to breastfeeding (I, Chaudron and Jefferson, 2000) because it is present in breast milk at 40% of the maternal serum concentration (American Academy of Paediatrics Committee on Drugs, 2000).

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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.

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.
- Estimated glomerular filtration rates (Morriss and Benjamin, 2008), thyroid function.
- Pregnancy test (in women of childbearing age).

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 (1.0–1.2 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, polydipsia, weight gain, cognitive problems, sedation or lethargy, impaired coordination, gastrointestinal distress, hair loss, benign leukocytosis, acne and edema. Lithium can precipitate and exacerbate psoriasis.
- 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%–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 (TSH) consider adding L-thyroxine.
- For persistent tremor consider adding propranolol.
- 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, hematological 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 (about 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/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/day, but all patients receiving daily doses higher than 45 mg/kg should be carefully monitored. However, a total dose of 1250 mg/day is the highest 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 thrombocytopenia 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, hemorrhagic 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 (FBC) 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 CBZ is drug–drug interactions. Induction of enzymes can reduce the effectiveness of coprescribed medications including antipsychotics, antidepressants and oral contraceptives (OC).

Dosing

- CBZ 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 to 1600 mg/day in routine clinical practice and should be as high as possible without producing adverse effects.

Long-term monitoring of laboratory values

- FBC, 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 thrombocytopenia, hyponatremia and (less commonly) hypo-osmolality.
- 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 CBZ analogue oxcarbazepine may be a useful alternative to CBZ 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. After that, 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 CBZ 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 0.01% (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 valproate's effects on hepatic metabolism.