PHARMACEUTICAL CARE

(13) MOOD DISORDERS: BIPOLAR CONDITIONS

By Karen Fraser, MSc, MRPharmS, Morag Martin, BSc, MRPharmS, Robert Hunter, MD, MRCPsych, and Steve Hudson, MPharm, FRPharmS

In this, the last of three articles on mood disorders, the treatment of bipolar disorders is considered. Previous articles addressed the implications of mood disorders for primary care and the treatment of depression

Bipolar mood disorders are usually treated in primary care with shared care arrangements with psychiatric specialists. A community pharmacy serving a typical population of 5,000 people might expect to provide prophylactic medication for about 20 patients with bipolar disorders.[1] These patients are likely to be well-known, individually, by their pharmacist. They are an important target group for pharmaceutical care in the community because the course of their illness extends over many years and treatment relies on the use of preventive medication with mood stabilisers, such as lithium, to avoid relapses. Bipolar patients have an increased morbidity and mortality risk because of potential self-neglect, accidental death and suicide. They are among the most likely patients to be admitted to hospital involuntarily and therefore represent a key target group for hospital pharmacists working with psychiatric specialists during acute hospital treatment.

The selection and trial of drug combinations and non-compliance are important issues in managing bipolar disorder.

CLINICAL FEATURES

Bipolar mood disorder is characterised by episodes of decreased activity and major depression (reviewed in earlier articles in this series[2,3]), interspersed with episodes of increased activity and mania (or hypomania, which is milder and free from psychotic features). The episodes of depression may last for between six months and a year, and the manic episodes may last for two weeks to four months. Manic behaviour includes poor judgement and overactivity, features that introduce chaos into a patient's life and can affect relationships and social functioning.[4] Bipolar mood disorder is characterised by the nature of the current episode, which can be manic, depressed, hypomanic, or mixed manic-depressive. In mixed episodes, there is rapid alternation or co-existence of symptoms of depression and mania. Mixed episodes are often the most disabling and present a higher risk of suicide than other forms.[5]

Mania is a discrete episode of abnormal, persistently elevated, expansive or irritable mood normally lasting more than a week. Manic episodes can be accompanied by delusions or hallucinations. Diagnosis requires the concurrent presence of at least three of the symptoms described in Panel 1.[6] The features of mania, and its milder form, hypomania, include increased activity and elation or dysphoria. In manic states, there is an elevation of mood that is out of keeping with the individual's circumstances, whereas in dysphoria there is irritability, which may manifest in the suspicion and blaming of others. Mania is marked by loss of attention span and of social inhibitions, with increased sexual or aggressive motivation, coupled with lack of insight and denial. The patient may experience heightened perception of colour and sounds and may become preoccupied with sensations such as textures and details of surfaces.[4,5] Psychosis can also be present, which lends further exaggeration to the manic symptoms and leads to greater risk of self-neglect.

Manic episodes that mimic bipolar disorder may be secondary to substance abuse, psychoactive medication (including precipitation by antidepressant medication, especially in those with a family history of bipolar disorder), head injury, and certain neurological/endocrinological disorders.[7] Bipolar disorder can be associated with other psychiatric co-morbidity, such as substance abuse, obsessive-compulsive disorder and panic disorder.

Diagnosis is often delayed and patients may have attempted to seek help over a period of years. It is most often first diagnosed in young adults and there is a similar prevalence in men and women. The condition does occur in children and adolescents, but is thought to be under-diagnosed and potentially confused with other behavioural disturbances. There is a greater risk of the illness, and of other mood disorders, among first degree relatives of people with bipolar disorder.

Ms Fraser is medicines information and research pharmacist, Ms Martin is principal pharmacist (clinical services) and Dr Hunter is consultant psychiatrist and director of research and development, Greater Glasgow Primary Care NHS Trust. Professor Hudson is Boots professor of pharmaceutical care, pharmaceutical care health service unit, department of pharmaceutical sciences, University of Strathclyde, Glasgow and Scottish Executive national specialist in pharmaceutical care

The mood swing usually occurs with an episode of depression immediately before or after an episode of mania. However, in a small minority (less than 5 per cent of patients), the manic episodes are not accompanied by periods of depression. Bipolar disorder is more often identified in men from an initial manic episode and in women from a period of depression.[7] For each individual, a particular temporal pattern emerges and repeats itself. Untreated, there is a tendency over time for the interval between episodes to decrease.

Bipolar II disorder is a subgroup of bipolar disorder in which depressive symptoms are interspersed with episodes of hypomania. If hypomania goes unrecognised, the standard treatment of depressive symptoms with antidepressant drugs can trigger a full-blown bipolar disorder. Compared with patients with major depression, patients with bipolar disorder have more frequent episodes of illness and an increased suicide risk. A small minority of bipolar II patients go on to experience episodes of mania and to be recategorised as bipolar I.[5,7]

A subgroup of about 10–20 per cent of those with bipolar I and II, mainly women,

Panel 1: Symptoms of mania/hypomania[4,6]

Mania/hypomania is diagnosed by concurrent presence of at least three of the following:

- Grandiosity/inflated self-esteem
- Decreased need for sleep
- Talkativeness (pressured speech)
- Flight of ideas (rapidly racing thoughts and flitting of ideas)
- Marked distractibility
- Increased goal-directed activity/psychomotor agitation
- Excessive involvement in pleasurable activities without regard for negative consequences (examples are unrestrained buying sprees, sexual indiscretions, foolish business ventures)

Symptoms must be severe enough to impair function markedly, or require admission to hospital to prevent harm to self or others. The possibility of symptoms being caused by schizophrenia, schizoaffective disorder, or substance abuse must be excluded.

may experience or develop "rapid cycling", which is a pattern of four or more episodes a year, such that there may be no intervening asymptomatic periods.[6,8] The cause of rapid cycling is unknown but the condition can be associated with thyroid disorder and be triggered by the use of tricyclic, and perhaps other, antidepressant medication in the absence of mood stabilisers. Rapid cycling disorder responds less well than other forms of bipolar disorder to lithium, and so other treatments may be necessary, such as thyroid hormone and anticonvulsants.[7] Electroconvulsive therapy remains a treatment option for severe bipolar disorder and can be life-saving.[9]

A chronic, milder form of bipolar disorder persisting over several years is cyclothymic disorder, in which the symptoms of mild depression continuously alternate with hypomania but are not sufficiently marked to meet the separate diagnostic criteria for either condition.[5,6] The prevalence of cyclothymic disorder is similar to that of bipolar disorder itself.[7]

Drug treatment and prophylaxis

The psychopharmacological management of bipolar disorder relies on the prophylactic use of mood stabilising drugs (chiefly lithium, but anticonvulsants such as valproate and carbamazepine are also used as adjuncts or alternatives).[8] The mechanism of action of these drugs is thought to be through effects on ionic channels beyond postsynaptic receptors, but the precise action remains uncharacterised. Anticonvulsants are thought to interfere with ionic transfer and ultimately reduce excitatory glutamate and increase inhibitory gamma-aminobutyric acid (GABA).[10]

Lithium was the first psychotropic agent to be shown to prevent recurrent illness. It has a place in the acute treatment of mania/hypomania. Antipsychotic agents are also used in acute mania. Lithium is less effective in rapid cycling disorder and in treating mixed manic-depressive episodes. Antidepressant drugs (discussed in a previous article[3]) are used to treat episodes of depression but can exacerbate post-manic depression.[8] The use of electroconvulsive therapy is outside the scope of this article, but can help the treatment of both depressive and manic episodes.[9]

Table 1: Initial strategy for first manic episode: choice of regimen[18]

Clinical presentation	Preferred initial strategy	Alternative strategy
Mania with psychosis	Mood stabiliser plus antipsychotic	Mood stabiliser plus antipsychotic plus benzodiazepine
Dysphoric mania or true mixed mania*	Mood stabiliser alone	Mood stabiliser plus benzodiazepine or mood stabiliser plus antipsychotic
Euphoric mania†	Mood stabiliser alone or mood stabiliser plus benzodiazepine	Mood stabiliser plus antipsychotic
Hypomania	Mood stabiliser alone	Mood stabiliser plus benzodiazepine

**Dysphoric mania: patient has a manic episode and also meets two to four diagnostic criteria for depression but is below the threshold for diagnosis of a major depressive episode. True mixed mania: patient meets full criteria for both a manic episode and a major depressive episode*
†Euphoric mania: patient has a manic episode without features of depression

Evidence base and clinical guidelines

Since the evidence base for the treatment of bipolar disorder is incomplete (because of lack of formal studies), clinical guidelines must rely on expert consensus to fill gaps in recommendations. Lithium remains a first-line treatment in the management of both acute mania and prophylactic treatment of bipolar disorder. Studies dating back to the early 1970s have demonstrated the efficacy of lithium in controlling manic episodes in bipolar patients[11-15] and in maintenance treatment of bipolar disorder.[16,17]

A recent consensus guideline, the result of a survey of psychiatric opinion in the United States, provides a useful reference point for the treatment of mania. Tables 1 and 2 summarise the choice of strategies for the use of mood stabiliser (lithium or anticonvulsant regimens).[18] The guideline considers a mood stabiliser alone as the treatment of choice for mania or hypomania, combined with an antipsychotic for mania with psychosis. Benzodiazepines are the preferred adjunctive therapy for other types of mania. Valproate and lithium were selected as the clear standards of care. Valproate is preferred for mania that is mixed, dysphoric or includes psychosis. Lithium is the first-line choice for euphoric mania. Carbamazepine is described as "a very highly ranked second-line alternative for all subtypes of mania". Lamotrigine and gabapentin are only recommended by the consensus guideline for use when the choices in Table 2 fail or cannot be used. Use of topiramate, tiagabine and calcium channel blockers was less well supported.

Table 3 summarises the evidence base and the recommendations for the treatment and prophylaxis of bipolar disorder.

Table 2: Initial strategy for first manic episode: choice of mood stabiliser[18]

Clinical presentation	Preferred mood stabilisers	Alternative mood stabiliser
Mania with psychosis	1. Valproate* 2. Lithium	Carbamazepine
Dysphoric mania or true mixed mania	1. Valproate* 2. Lithium	Carbamazepine
Euphoric mania	1. Lithium 2. Valproate*	Carbamazepine
Hypomania	1.Lithium 2.Valproate*	Carbamazepine

**Valproate is included in the US guidelines as divalproex, the US approved name for valproic acid (semisodium valproate) which was licensed in the UK in January 2001, as Depakote*

Treatment of acute mania / hypomania

Instigation or optimisation of a mood stabiliser is recognised as a first step in the management of acute manic and hypomanic states. Any drugs which can induce mania, (such as antidepressants) should be immediately withdrawn.

Lithium High plasma lithium concentrations (up to 1.5mmol/L) may be required in the short term, with doses reduced to achieve 0.6–1.2mmol/L once mood is stabilised. Time to remission of symptoms appears to be strongly related to rapid achievement of therapeutic drug levels. Onset of action of lithium is up to five to seven days, or more to achieve the full effect, and adjunctive treatment with benzodiazepines and antipsychotic agents is usually necessary.[19,20] Poor responses to lithium have been attributed to differences in pathophysiology of bipolar disorder reflected in higher frequency of episodes, more severely ill patients with concomitant depression and mania, frequent previous psychiatric admissions, social deprivation and current alcohol and drug abuse.[21-23]

Valproate Valproate has been shown to be effective in the management of acute mania, including management of patients who have been unresponsive to lithium.[24] Until recently, there was no licensed valproate product for this indication in the UK, although sodium valproate has been used off-label for many years by psychiatrists. It remains to be established how this practice will be changed by the introduction of a licensed product, semisodium valproate (Depakote), for acute mania in January 2001.

Clinically, the proposed advantage of semisodium valproate is more rapid achievement of therapeutic plasma concentrations, which may be advantageous in terms of the speed of onset of symptom control.[25] Onset of action of valproate is related to the attainment of therapeutic blood concentrations, so more rapid control of manic symptoms

may be achievable by the use of a loading dose.[26,27] The optimum valproate plasma concentration in acute mania appears to be in the range 50–125mg/L[26] with 50–100mg/L generally recommended as the reference range. As with lithium and carbamazepine, adjunctive treatment with benzodiazepines/antipsychotics may also be necessary when valproate is used in acute mania or hypomania.[28]

There is limited evidence to support the use of valproate in combination with either lithium[29] or carbamazepine[30] in cases where either drug alone has lacked efficacy in bipolar disorder. Valproate may be more effective than lithium in particular patient groups, such as those with mixed mania, rapid cycling and co-morbid substance abuse. Indeed, valproate has been shown to be effective in patients who are refractory to both lithium and carbamazepine.[31] However, lithium may be more effective in severe bipolar disorder.

Carbamazepine There have been five randomised controlled trials that have demonstrated comparable efficacy of carbamazepine with lithium in the treatment of acute mania.[25] However, in the UK, carbamazepine is licensed only for prophylactic treatment of bipolar disorder and not for acute mania, although its use in clinical practice is well documented.[28] Plasma concentrations of carbamazepine of 8–12mg/L are recommended, and adjunctive benzodiazepine/antipsychotic treatment is usually required in the acute phase. In a four-week double-blind study, comparing carbamazepine and lithium in a group of patients with mania, significant improvement was seen in both treatment groups.

Lithium is considered to be more consistently effective in a heterogeneous group of patients with mania, but use of carbamazepine is well-justified in lithium non-responders.[32] It has been suggested that patients of mania-dominant type, with isolated occurrence of manic and depressive episodes, onset of illness below age 30, and with atypical symptoms, might benefit particularly from carbamazepine.[33] Combination treatment with lithium and carbamazepine has been shown to be useful in the management of acute mania.[34,35]

PROPHYLAXIS OF BIPOLAR DISORDER

Lithium Continuation of prophylactic lithium therapy in bipolar disorder can decrease the incidence of relapses and increase intervals between episodes of acute mania.[36] It has been suggested that regular long-term lithium treatment can also reduce the excess mortality of patients with recurrent affective disorders by protecting against suicidal behaviour.[37] Controlled studies have been undertaken to demonstrate the efficacy of lithium prophylaxis of bipolar disorder, although the effects of abrupt withdrawal from lithium have been a source of criticism in the studies.[38] Data now suggest that a gradual tapering of the dose produces a much lower relapse rate.[39,40] Lithium-discontinuation studies that employ a gradual withdrawal of lithium after approximately one year of lithium therapy are needed. The length of prophylactic treatment with lithium is controversial. Effectiveness beyond one year has been questioned.[41] In some studies, approximately 44–50 per cent of patients relapsed during the first year, regardless of compliance.[21,22] However, other work has

TABLE 3: EVIDENCE BASE FOR MOOD STABILISERS IN BIPOLAR DISORDER

Evidence based findings	Recommendations
ACUTE MANIA/HYPOMANIA	
Mood stabilisers (lithium,[11-13,15] carbamazepine[25,28] and valproate[24,25]) are effective in the management of acute mania/hypomania. Time to remission of symptoms appears to be related to rapid achievement of therapeutic plasma drug concentrations[26,27,50]	Treatment with a mood stabiliser should be commenced or optimised. Choice of mood stabiliser may be governed by previous response, subtype of mania and co-existing illness. Lithium and valproate (as semisodium valproate) are licensed for acute mania and hypomania Carbamazepine is licensed only for prophylaxis of bipolar disorder, but its clinical use in acute mania is well documented Recommended therapeutic plasma concentration ranges: ● Lithium 0.5–1.0 mmol/L ● Carbamazepine 8–12mg/L(34–50µmol/L) ● Valproate 50–100mg/L (350–700µmol/L)
Onset of action of mood stabilisers is not immediate and adjunctive treatment is usually required in the initial stages of management of a manic/hypomanic episode[58]	Benzodiazepines and antipsychotics are often required as initial adjunctive treatment in acute mania/hypomania. Choice depends on the presenting symptoms, for example, antipsychotics in the case of co-existing psychosis. Adjunctive treatment should be reassessed and withdrawn after symptoms have resolved
Antidepressants can precipitate a manic/hypomanic episode[58]	Any antidepressants should be withdrawn in acute mania/hypomania
Combinations including lithium and carbamazepine,[34,35] lithium and valproate[29], and valproate and carbamazepine[30] have been investigated in the management of acute mania/hypomania	Combinations of mood stabilisers should be tried where single agents have proven ineffective in acute mania/hypomania
Limited evidence exists to support the use of other anticonvulsants (gabapentin,[45] lamotrigine,[47,48] or topiramate[49]) in refractory cases of mania/hypomania	These newer anticonvulsants are not licensed for the treatment of mania and they should only be initiated by specialists in refractory cases
MAINTENANCE TREATMENT	
Continuation of prophylactic treatment with a mood stabiliser can decrease the incidence of relapses and increase intervals between episodes of acute mania.[51,52] Regular long-term lithium treatment may reduce excess mortality seen with recurrent affective disorders by protecting against suicidal behaviour[37]	The mood stabiliser used in acute management of mania/hypomania should be continued as prophylaxis. Valproate is not currently licensed for maintenance treatment in bipolar disorder, but its use is well documented clinically. Patients with bipolar disorder have a high relative risk of suicide and prophylactic treatment with mood stabilisers is important in reducing this risk
Duration of maintenance treatment is controversial.[41,42] If treatment is discontinued too soon, premature recurrence of mania can result.[42] Indeed, it has been shown that regular lithium use over five years greatly reduces the time spent in hospital, but irregular use leads to a much poorer outcome[53]	For lithium, there is support for treatment to be continued for at least two years
Poor compliance with prophylactic treatment is the main reason for lithium failure.[54] Specialised care, such as lithium clinics, can improve outcomes	Once a patient is stabilised on lithium, regular monitoring of plasma lithium concentration is required (every three months). During maintenance treatment, lithium levels of 0.5–1.0mmol/L are considered to be safe and effective. Community pharmacists have an important role to play in helping to assist compliance and providing education on lithium
Combinations of mood stabilisers can be effective in prophylactic management of bipolar disorder[31]	If combination treatment is required in the acute treatment of mania, then the combination should be continued as maintenance treatment
There is limited evidence of efficacy of the newer anticonvulsants as prophylactic treatment of bipolar disorder[45,48,49]	Newer anticonvulsants are not licensed for the maintenance treatment of bipolar disorder and are only initiated by specialists

suggested that treatment with lithium should be continued for at least two years, and preferably three years, as a minimum.[42] Discontinuation of treatment before two years can risk premature recurrence of mania.

Valproate Case studies and open trials have suggested that valproate is effective in the prevention of mania.[43] Indeed, valproate has been shown to be effective in patients who have been refractory to both lithium and carbamazepine.[31]

Carbamazepine The efficacy of long-term carbamazepine has been addressed in several small studies. In one 20-month study of 24 patients, 12 of whom had previously been unresponsive to lithium, 80 per cent demonstrated persistent improvement with carbamazepine and side effects were mild and infrequent.[44]

In a double-blind study of 52 patients with bipolar disorder, lithium and carbamazepine had an approximately equal, but less than adequate, prophylactic efficacy in overall bipolar illness.[31] In the first year, patients were randomly assigned to treatment with lithium or carbamazepine, and then crossed over to the other drug in the second year. In the third year, patients received the two drugs in combination. A marked or moderate improvement was achieved in 31–33 per cent of patients on carbamazepine or lithium alone, and in 55 per cent on the combination. Lithium was found to be superior in the prophylaxis of mania although certain individuals showed improvement on one drug after poor response to the other. Rapid cycling patients did poorly on monotherapy and tended to improve on combination therapy.

Other anticonvulsants There is limited evidence on the use of the anticonvulsants gabapentin, lamotrigine and topiramate in the management of bipolar disorder. It should be noted that these drugs are unlicensed for this indication and they are only used by specialists in refractory cases.

Gabapentin has been reported to be effective in treating mania and hypomania in bipolar and schizoaffective disorders in an open study of 22 patients.[45] Gabapentin dose was titrated upwards by 300mg/day every four days to a maximum dose of 2,400mg/day, depending on tolerance. The mean dose used was 1,440mg/day. Mood stabilisers such as lithium, carbamazepine, and valproate were gradually withdrawn over four weeks, but benzodiazepines and antipsychotic drugs were continued during the study period. Significant improvements were seen after 16 weeks of treatment, with sedation being the most common side effect. Positive results with gabapentin were also obtained in an open study of 28 patients with bipolar disorder who were refractory to treatment with all standard mood stabilising drugs. In this study, gabapentin was used in combination with anxiolytic agents, antidepressants, antipsychotics and other anticonvulsants.[46]

Lamotrigine, in doses of 50–200mg daily, has been reported to be effective in a randomised placebo-controlled trial in patients with bipolar I disorder.[47] A sustained effect has also been demonstrated in treatment-resistant cases where reduction in manic symptoms was obtained with lamotrigine over eight weeks, with benefits maintained for 48 weeks. Improvement in depressive symptoms was also shown.[48] There is recognition of the need for comparative studies of lamotrigine with established mood stabilising agents.

The evidence for topiramate in bipolar disorder is limited, although promising results were demonstrated in a retrospective study of patients with mood disorders refractory to standard treatments.[49]

Panel 2: Therapeutic drug monitoring for lithium

Lithium carbonate dose regimens

- Camcolit treatment: 1.5–2.0g (elderly 0.5–1.0g) daily
  Camcolit prophylaxis: 0.5–1.2g (elderly 0.5–1.0g) daily
  (given as Camcolit 250 in divided doses, or Camcolit 400 in single or divided doses)
- Liskonum treatment: 450–675mg (elderly 225mg) twice daily
  Liskonum prophylaxis: 450mg (elderly 225mg) twice daily
- Priadel treatment and prophylaxis: 400–1,200mg daily in single or divided doses (400mg twice daily in elderly and those less than 50kg)

Lithium citrate preparations

- Lithium citrate is available in liquid form — see manufacturers' summary of product characterisitics

Oral absorption

- Bioavailability 100 per cent (normal release), 60–90 per cent (modified release)
- Bioavailability affected by diarrhoea
- Peak plasma concentrations at approximately two to two and a half hours (Camcolit and Priadel) and three to five hours (Litarex, Liskonum)

Distribution

- Volume of distribution: adults 0.7–1.0 L/kg, 0.42L/kg in obese adults
- The distribution half life is approximately one hour and protein binding is zero

Clearance

- Eliminated entirely by kidneys (95 per cent by glomerular filtration with 80 per cent reabsorption)
- Adults: 0.25 x creatinine clearance (Cl_{Cr})
- Elimination half life 18–36 hours

Plasma concentration monitoring

- Samples should be taken at least 12 hours after dose (12 hour lithium standard):
  Therapeutic range (general) 0.4–1.2mmol/L
  Acute mania 0.8–1.5 mmol/L (delayed onset of up to four to five days)
  Maintenance therapy 0.5–1.0 mmol/L (delayed onset of up to several months)
- Avoid concentrations >1.5mmol/L, severe toxicity >2.0 mmol/L.
- Check plasma concentrations four to seven days after start of treatment then weekly until constant dose is maintained for more than four weeks, then every three months
- Monitor thyroid and renal function

Individual patient care

The care of patients with bipolar disorder is shared between the psychiatric and primary care teams.[8] Because of the specialised drugs used, pharmacists in primary care will be aware of patients receiving treatment for bipolar disorder from their patient medication records. Pharmacists have the opportunity to develop their contributions through their relationships with patients with bipolar disorder and their relatives, and with patient support groups. Patients with bipolar disorder are often well-informed about their condition and experienced about the effects of drug treatment on their own behaviour patterns. Nevertheless, it is important to address any misconceptions about the disease or the drug therapy.

The management of lithium treatment, in particular, is a focal point for the use of the pharmacist's patient medication record in monitoring for drug interactions, unwanted effects and signs of toxicity. Poor compliance with prophylactic treatment is the main reason for lithium failure. Specialised care, such as lithium clinics, can improve outcomes.[54] Different perceptions of patients with bipolar disorder complicate the patients' commitment to adhere to treatment. The description of life on lithi-

TABLE 4: PHARMACEUTICAL CARE IN BIPOLAR MOOD DISORDERS

Stage of treatment	Actions	Points to consider at each stage
Treatment plan ● Patient comprehension/ active participation ● Patient's characteristics ● Indication (the need for each drug) ● Drug history ● Choice of medication ● Contraindication/ interaction ● Conformity to guidelines ● Continuity of care	*Verify the plan in respect of* ● Patient's characteristics ● Medication suitability ● Patient's needs for education ● Concordance and agreed expectations *Modify the plan to address* ● Specific educational needs ● Need for individualisation of treatment plan	● Consider concomitant physical disorders that are associated with or which complicate the mood disorder ● Social circumstances, family environment, family stigma and support ● Alert the patient to common side effects of medication and provide reassurance ● Verify accurate drug history, including any prior use of antidepressants and other psychoactive agents, and over-the-counter (OTC) products ● Identify other medication that can cause or aggravate mood disorders ● Identify co-morbid states that complicate treatment and its evaluation, eg, thyroid disorders ● Collaborate with other team members to share information to alert the team to those at risk of overdose ● Provide advice on request about patient support groups ● Note and respond to the need for personalised information. Product's patient information leaflet (especially those used primarily as anticonvulsants) may not adequately refer to use in bipolar disorder
Implementation ● Dose ● Frequency ● Timing ● Compliance ● Clinical signs ● Laboratory markers	*Monitor the patient for* ● Continuing suitability of drug/dose regimen ● Signs/symptoms of effectiveness and toxicity *Adjust the process by* ● Further individualisation in response to monitoring	● The irregular course of the disease requires the inclusion of the patient in self-monitoring and good documentation of symptoms ● Ensure individualisation of medication dose using information and preferences from patient ● Secure support and information from relatives and friends to allow them to supervise medication and report on symptoms when patient is ill ● Equally, be alert to possibility of patient receiving misconceptions about the disease and its treatment from others ● Make checks of compliance and maintenance of concordance. Written treatment contracts may support implementation of treatment ● Make checks of handling of medicines and safety of storage ● Carry out specific monitoring for renal function in conjunction with therapeutic drug monitoring ● Specific drug-induced syndromes such as syndrome of inappropriate antidiuretic hormone secretion (SIADH) which is particularly associated with carbazamepine ● Checks for drug interactions, including OTC products
Clinical outcome ● Therapeutic benefit ● Safety ● Unwanted symptoms ● Recorded adverse drug reactions	*Confirm evidence of treatment success* ● Reassure patient in relation to agreed expectations *Prompt a review from* ● Identification of treatment failure ● Newly identified patient needs ● Sharing information and discussion of implications with the prescriber and other team members	● Acknowledge adverse effects as perceived by patients ● Recognise persistent side effects requiring clinical review of the therapeutic plan ● Confirm adequate duration of acute treatment course ● Recognise symptomatic changes to allow early referral for a clinical review of the patient's needs

um by Jamison[55] provides revealing insights. Patients may associate lithium treatment with unwanted physical and behavioural effects so that they may be ambivalent towards lithium and see it not only as bringing relief from perhaps a frenetic behaviour pattern, but also negatively influencing personality and lifestyle.

Regular three-monthly monitoring of lithium blood concentrations is required and levels of 0.5–1.0mmol/L are generally considered to be safe and effective (see Panel 2). Regular lithium use for longer than five years greatly reduces the time spent in hospital, but irregular use leads to a much poorer outcome.[53] Community pharmacists have an important role to play in their relationship with patients on lithium, through monitoring for unwanted effects and by helping with the education of patients to help them achieve good compliance. The lithium card, available from the National Pharmaceutical Association, instructs patients on how to take lithium prepa-

Panel 3: Monitoring of patients on lithium

- Lithium blood levels should normally be measured on a three-monthly basis (for patients on established treatment)
- The blood sample should be taken at the same time interval post-dose on each occasion (ideally 12–18 hours)
- On a yearly basis, the following should be checked: urea and electrolytes, renal function (serum creatinine/creatinine clearance and urine tested for presence of blood or protein), thyroid function and weight, blood pressure, pulse
- Certain patients may require more frequent monitoring, eg, the elderly, those taking interacting medication and those with medical co-morbidity (especially impaired renal, thyroid or cardiac function)

Panel 4: Lithium preparations

- Patients should receive the same brand/preparation of lithium on each occasion, because different brands/preparations vary in bioavailability, leading to potential alterations in lithium level
- All prescriptions should be written in proprietary format (brand name). Ensure that this information is recorded in the patient medication record and query any prescription which stipulates a different brand/preparation
- More frequent monitoring of lithium blood levels is required if switching between lithium brands or between tablet and liquid formulations
- Lithium salts are not equivalent to one another, ie, lithium carbonate 200mg is not equivalent to lithium citrate 200mg
- Ensure a lithium card is issued to each patient at the outset of treatment and that appropriate counselling points are discussed. (Cards are available from National Pharmaceutical Association Services, 38–42 St Peters street, St Albans, Hertfordshire AL1 3NP.)

Case 1: Patient BM, female, 38 years
weight 65kg, height 1.67m

Presenting complaint
Vomiting and diarrhoea
Sprained wrist, unresponsive to ibuprofen

Past medical history
Bipolar disorder — controlled on lithium
Mood swings have been controlled for the past two years

Current drug treatment
Priadel tablets (modified release lithium carbonate), daily dose 1,000mg
Recent plasma lithium 0.8mmol/L
Ibuprofen tablets 200mg *prn* as an over-the-counter (OTC) purchase made one week ago

Non-steroidal anti-inflammatory drugs (NSAIDs) affect renal prostaglandins and lithium clearance resulting in an increase in plasma lithium concentration which risks toxicity. Ibuprofen is a particular problem because it is widely available on general sale. Sulindac is an NSAID reported either to reduce or to have no effect on plasma lithium

Vomiting and severe diarrhoea are signs of lithium toxicity. Symptoms also include tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching. There is also muscle weakness, lack of co-ordination and drowsiness or lethargy, progressing to giddiness with ataxia

Plasma samples are taken 12 hours post-dose to ensure equilibration. The target lithium plasma concentration range is generally 0.5–1.0 mmol/L, although a lower reference range of 0.4–0.8 mmol/L may be used to guide long-term treatment

Single dose of lithium preferred to minimise renal toxicitiy. Night time dosefacilitates blood sampling in morning (12 hours after night-time dose)

Paracetamol, aspirin or codeine containing analgesic preparations are alternatives which do not interact with lithium

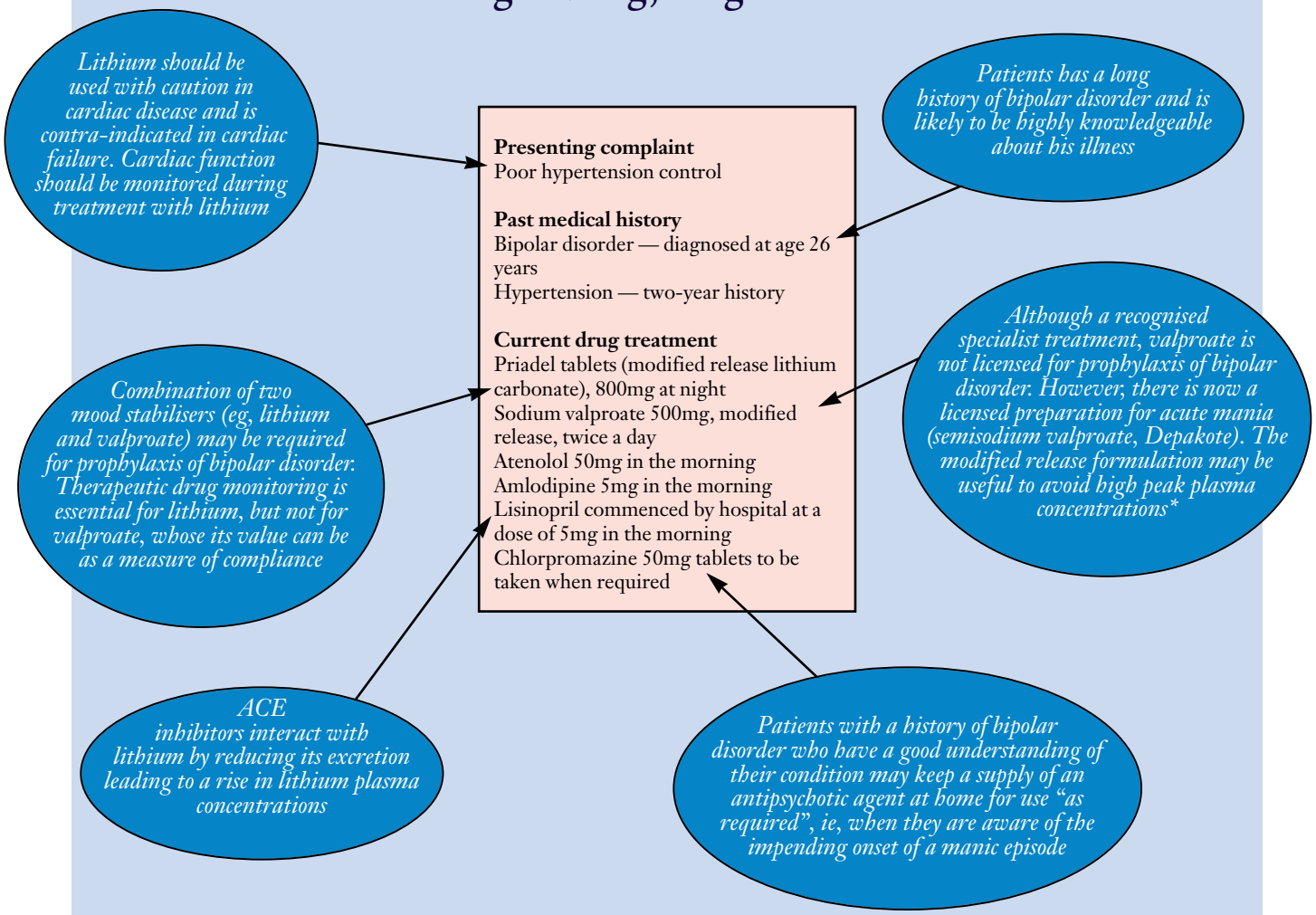
Once patient is stabilised, lithium levels should continue to be monitored on a three-monthly basis. If an NSAID is considered essential, plasma lithium concentrations should be monitored more frequently

Lithium toxicity can be fatal. At lithium concentrations above 2–3 mmol/L, there may be a large output of dilute urine, with increasing disorientation, seizures, coma and death

PHARMACEUTICAL CARE PLAN

CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1. Verify drug history (especially OTC products)	Eliminate possible interaction as cause of lithium toxicity. NSAIDs such as ibuprofen can interact with lithium to increase lithium plasma concentrations
2. Monitor for signs of lithium toxicity	Check for gastrointestinal symptoms, drowsiness and musculoskeletal signs of lithium toxicity (coarse tremor)
3. Prompt review of suspected lithium toxicity	Signs of toxicity are an indication for urgent referral and measurement of plasma lithium
4. Prompt review of analgesic	Paracetamol-, aspirin- or codeine-containing analgesic preparations are alternatives which do not interact with lithium. If an NSAID is considered essential, increased frequency of blood level monitoring is necessary
5. Monitor lithium plasma concentration	When patient is stabilised, lithium levels should be monitored every three months (therapeutic range 0.5–1.0mmol/L). Check that levels are recorded on the patient's lithium treatment card
6. Monitor patient compliance with lithium	Check for continued adherence to lithium; plasma levels can be used as a guide. Counsel the patient to be careful to adhere to the prescribed dose
7. Monitor renal and thyroid function	Plasma creatinine, electrolytes and thyroid function tests should be monitored at least once a year
8. Verify patient's comprehension	Ensure a lithium treatment card is issued. Use it to emphasise counselling points, including highlighting signs of a high lithium level and raising awareness of potential drug interactions, especially those with OTC products. Stress the importance of checking for the name of the active drug contained in a proprietary product. Explain the long-term nature of prophylactic treatment

Case 2: Patient CD, male, 54 years
weight 74kg, height 1.80m



PHARMACEUTICAL CARE PLAN

CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1. Verify drug history	As antihypertensive therapy is changed, check for possible interactions, particularly with lithium because of its narrow therapeutic range. ACE inhibitors, such as lisinopril, can reduce lithium excretion leading to a potential increase in plasma concentration
2. Monitor for signs of lithium toxicity	Check for gastrointestinal symptoms, drowsiness and musculoskeletal signs of lithium toxicity
3. Monitor mood stabiliser plasma concentrations	Lithium levels should be monitored every three months (therapeutic range 0.5–1.0mmol/L), but more frequent monitoring may be required in the presence of a newly prescribed potentially interacting agent. Valproate levels are not as essential in terms of toxicity monitoring, but may be a useful guide to compliance, or for investigating lack of efficacy. The recommended valproate plasma range in bipolar disorder is 50–100mg/L
4. Verify patient's comprehension	Ensure lithium treatment card is issued and use it to emphasise counselling points. Valproate is not licensed for the prophylaxis of bipolar disorder, so ensure that the patient is aware of this specialised use because the manufacturer's product information leaflet will only refer to the licensed indication of epilepsy, which might alarm the patient. Patient information leaflets on valproate in bipolar disorder may be provided by specialist psychiatric pharmacies and can be purchased from the UK Psychiatric Pharmacists' Group (UKPPG)†
5. Monitor for signs of deterioration in mental state	Patients with bipolar disorder who have a good understanding of their condition may be prescribed "as required" antipsychotic drugs (such as chlorpromazine) to take if they recognise signs of an impending manic episode. Monitoring for increased frequency of repeat prescriptions for antipsychotic agents may provide a guide to a potential deterioration in mental state

** See Maudsley Prescribing Guidelines 6th edition, 2001*[59]
†see UKPGG website (www.ukppg.org.uk)

Panel 5: Side effects and toxicity of lithium

- Common side effects of lithium (which are usually dose dependent) include: gastrointestinal disturbance, weight gain, oedema, fine tremor, polyuria, polydipsia and hypothyroidism. These effects may be transient and consideration should be given to a dose reduction to relieve such problems
- Signs of lithium toxicity include: vomiting and severe diarrhoea, tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching. Also, muscle weakness, lack of co-ordination, drowsiness or lethargy progressing to giddiness with ataxia. Convulsions and ECG changes may occur
- If a patient shows signs of lithium toxicity, lithium must be stopped and the patient referred to a doctor immediately

TABLE 5: SUMMARY OF LITHIUM DRUG INTERACTIONS[57,58]

Drugs implicated	Mechanism and effect
ACE inhibitors/ angiotensin II antagonists	Exact mechanism of interaction unclear. Lithium toxicity reported due to an increase in lithium levels; renal toxicity can also occur
Antacids	Sodium-containing antacids can cause increased lithium excretion leading to a decrease in lithium levels and reduced effectiveness
Antidepressants: selective serotonin reuptake inhibitors and monoamine oxidase inhibitors	SSRIs: neurotoxicity, increase in lithium levels, lithium toxicity and serotonin syndrome have been reported with certain SSRIs MAOIs: increase in brain serotonin levels and serotonin syndrome reported
Antiepiletics	Carbamazepine: neurotoxicity reported Phenytoin: limited evidence of lithium toxicity
Antipsychotics	Central nervous system (CNS) toxicity has been reported with a number of antipsychotics
Calcium channel blockers	Possible synergistic decrease in calcium ion transport, leading to neurotoxicity, worsening of mania and bradycardia
Diuretics	Decreased lithium clearance leading to increased lithium concentrations and possible toxicity has been reported, particularly with thiazide diuretics and also with loop and potassium-sparing diuretics Acetazolamide has been reported to increase lithium excretion, leading to decreased lithium levels and a loss of efficacy
Methyldopa	Increased CNS response to lithium leading to increased risk of lithium toxicity and neurotoxicity
Metronidazole	Increased lithium levels reported; some reports of toxicity
Non-steroidal anti-inflammatory drugs, COX-2 inhibitors	Decreased lithium clearance leading to increased lithium concentrations and possible toxicity. No such interaction reported with aspirin or sulindac
Theophylline	Increased lithium clearance leading to reduction in lithium levels and reduced efficacy

rations, what to do if a dose is missed, and what side effects to expect. It also explains why regular blood tests are important and warns that some medicines and illnesses can change plasma lithium concentrations. Specialised patient information leaflets are available from the UK Psychiatric Pharmacists Association (see www.ukppg.org.uk). The educational role in the delivery of pharmaceutical care is directed at both drug treatment and general support.

Table 4 summarises the types of pharmaceutical care issues arising from the management of bipolar disorders. Table 5 lists lithium drug interactions, and Panels 3, 4 and 5 cover monitoring of patients on lithium, types of lithium preparation and side effects of lithium.

Patients with bipolar disorder have a number of multidisciplinary contacts. Continuity of support is essential, with co-ordination of patient monitoring and reinforcement of educational messages. Teaching patients to recognise early symptoms of manic relapse, and to seek early treatment, is associated with important clinical improvements in time to first manic relapse and social functioning, and in employment.[56] Local pharmacy networks can develop and integrate pharmaceutical support to patients with bipolar disorder. Locally agreed protocols offer the means of achieving consistent monitoring of patient care across the primary and secondary care settings. Patients with bipolar disorder are an important target group for the development of pharmaceutical care jointly between hospital pharmacy specialists and local community pharmacists.

ACKNOWLEDEGMENTS The authors thank Dr Alison Thomson (principal pharmacist, clinical pharmacokinetics unit, Western Infirmary, Glasgow) and Mrs Joy Nicholson (principal pharmacist, Royal Edinburgh Hospital) for useful discussions in the preparation of this article and for provision of information from local protocols.

REFERENCES

1. Meltzer H, Gill B, Petticrew M. The prevalence of psychiatric morbidity among adults living in private households. OPCS surveys of psychiatric morbidity in Great Britain, Report 1. London: HMSO; 1995.
2. Fraser K, Martin M, Hunter R, Hudson S. Mood disorders: implications for primary care. Pharm J 2001;266:259-62.
3. Fraser K, Martin M, Hunter R, Hudson S. Mood disorders: drug treatment of depression. Pharm J 2001;266:433-42.
4. Gelder M. Oxford textbook of psychiatry. 3rd ed. Oxford: Oxford University Press; 1996.
5. World Health Organization. The International Classification of Diseases (ICD-10) classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva: WHO; 1992.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Volume 4. 4th ed. Washington, DC: American Psychiatric Press; 1994.
7. Agency for Health Care Policy and Research. Clinical practice guideline number 5: depression in primary care: Volume 1. Detection and Diagnosis. Rockville MD: AHCPR; 1993.
8. Young H, Macritchie KAN, Calabrese JR. Treating bipolar affective disorder. BMJ 2000;321:1302-3.
9. Fink M. ECT is effective in bipolar disorder. BMJ 2001;322:365.
10. Stahl SM. Essential neuropharmacology. Neuroscientific basis and practical applications. 2nd ed. Cambridge: Cambridge University Press; 2000.
11. Prien RF, Caffrey E, Klett CJ. Prophylactic efficacy of lithium carbonate in manic-depressive illness: report of the Veterans' Admission and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1973;28:337-41.
12. Johnson G, Gurshon S, Burdock EI, Floyd A, Hekimian L. Comparative effects of lithium and chlorpromazine in the

treatment of acute manic states. Br J Psychiatry 1971;119:267.
13. Lerner J, Schlossberg E. Lithium in psychiatric therapy. J Am Geriatr Soc 1971;19:423-6.
14. Platman SR. A comparison of lithium carbonate and chlorpromazine in mania. Am J Psychiatry 1970;127:351-3.
15. Schlagenhauf G, Tupin J, White RB. The use of lithium carbonate in the treatment of manic psychoses. Am J Psychiatry 1966;123:199-207.
16. Stallone F, Shelly E, Mendlewicz J. The use of lithium in affective disorders III. A double-blind study of prophylaxis in bipolar illness. Am J Psychiatry 1973;130:1006-10.
17. Larson C, Kochar MS, Wang RI. Efficacy and safety of lithium carbonate in treatment of manic depressive illness. J Clin Pharmacol New Drugs 1972;12:459-64.
18. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. Expert consensus guideline series: Medication treatment of bipolar disorder. McGraw Hill, 2000. Postgrad Med special issue.
19. Modell JG, Lennox RH, Weiner S. Inpatient clinical trial of lorazepam for the management of manic agitation. J Clin Psychopharmacol 1985;5:109-13.
20. Soares JC, Mallinger AG, Gershon S. The role of antipsychotic agents in the treatment of bipolar disorder patients. Int J Clin Psychopharmacol 1997;12:65-76.
21. O'Connell RA, Mayo JA, Flatow L. Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991;159:123-9.
22. Mander AJ. Is lithium justified after one manic episode? Acta Psychiatr Scand 1986;73:60-7.
23. Swann AC, Secunda SK, Katz MM. Lithium treatment of mania: clinical characteristics, specificity of symptom change, and outcome. Psychiatry Res 1986;18:127-41.
24. Prasad AJ. The role of sodium valproate as an anti-manic agent. Pharmatherapeutica 1984;4:6-8.
25. Keck PE, McElroy S, Strakowski AM. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. J Clin Psychiatry 1998;56(Suppl 6):74-81.
26. Keck PE, McElroy S, Tugrul KC, Bennett JA. Valproate oral loading in the treatment of acute mania. J Clin Psychiatry 1993;54:305-8.
27. Bowden CL, Janicak PG, Orsulak P, Swann AC, Davis JM, Calabrese JR. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996;153:765-70.
28. Taylor DM, Duncan D. Doses of carbamazepine and valproate in bipolar affective disorder. Psychiatr Bull 1997;21:221-3.
29. Solomon DA, Ryan CE, Keitner G. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. J Clin Psychiatry 1997;58:95-9.
30. Schaff MR, Fawcett J, Zajecka JM. Divalproex sodium in the treatment of refractory affective disorders. J Clin Psychiatry 1993;54:380-4.
31. Denicoff KD, Smith-Jackson JE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997;58:470-8.
32. Lerer B, Moore N, Meyendorff E. Carbamazepine versus lithium in mania: a double-blind study. J Clin Psychiatry 1987;7:130-2.
33. Okuma T. Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology 1993;27:138-45.
34. Kramlinger KG, Post RM. Adding lithium carbonate to carbamazepine: antimanic efficacy in treatment-resistant mania. Acta Psychiatr Scand 1989;79:378-85.
35. Woods M. Carbamazepine for bipolar disorder. Drug Intell Clin Pharm 1986;20:49-52.
36. Mander AJ, Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. Lancet 1988;2:15-7.
37. Muller-Oerlinghausen B, Wolf T, Ahrens B. Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the International Group for the Study of Lithium-treated patients (IGSLI). Acta Psychiatr Scand 1996;94:344-7.
38. Coryell W, Winokur G, Solomon D, Shea T, Leon A, Keller M. Lithium and recurrence in a long-term follow-up of bipolar affective disorder. Psycholog Med 1997;27:281-9.
39. Baldessarini RJ, Tondo L. Recurrence risk in bipolar manic-depressive disorders after discontinuing lithium maintenance treatment: an overview. Clin Drug Invest 1998;15:337-51.
40. Baldessarini RJ Tondo L, Faedda GL. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996;57:441-8.
41. Silverstone T, McPherson H, Hunt N. How effective is lithium in the prevention of relapse in bipolar disorder? A prospective naturalistic follow-up study. Aust NZ J Psychiatry 1998;32:61-6 .
42. Goodwin GM. Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. Br J Psychiatry 1994;164:149-52.
43. Calabrese JR, Markovitz PJ, Kimmel SE, Wagner SC. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. J Clin Psychopharmacol 1992;12(Suppl):S53-6.
44. Stuppaeck C, Barnas C, Miller C. Carbamazepine in the prophylaxis of mood disorders. J Clin Psychopharmacol 1990; 10:39-42.
45. Cabras PL, Hardoy J, Hardoy MC. Clinical experience with gabapentin in patients with bipolar or schizoaffective disorder: results of an open-label study. J Clin Psychiatry 1999; 60:245-8.
46. Schaffer DB, Schaffer LC. Gabapentin in the treatment of bipolar disorder. Am J Psychiatry 1997;154:291-2.
47. Calabrese JR, Bowden C, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79-88.
48. Calabrese JR, Bowden C, McElroy SL, Cookson J, Andersen J, Keck PE Jr et al. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. Am J Psychiatry 1999; 156:1019-23.
49. Marcotte D. Use of topiramate, a new antiepileptic as a mood stabilizer. J Affective Disord 1998;50:245-51.
50. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar disorder. J Clin Psychiatry 1998;59:151-8.
51. Suppes T, Baldessarini R, Faedda G. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082-8.
52. Tondo L, Baldessarini R, Hennenm J. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. Am J Psychiatry 1998;155:638-45.
53. Maj M, Pirozzi R, Magliano L. Long-term outcome of lithium prophylaxis in bipolar disorder: A five-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30-5.
54. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness. Efficacy, effectiveness and efficiency. Br J Psychiatry 1994;164:741-6.
55. Jamison KR. An unquiet mind. Basingstoke, Oxford: Picador; 1996.
56. Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 1999;318:149-53.
57. British National Formulary (number 40). London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2000.
58. CD ROM, Drug evaluation monograph. Lithium. Denver, Colorado: Micromedex Inc; Expiry 06/2001.
59. Taylor D MD, McConnell H, Kerwin R. The Maudsley Prescribing Guidelines (6th ed). London: Martin Dunitz; 2001.
60. American Psychiatric Association. Practice guideline for bipolar disorder. Am J Psychiatry 1994;151:1-36.