The aim of drug treatment in bipolar disorder is to manage acute episodes of mania, hypomania and depression and, in the longer term, prevent relapse. The second article in this month’s special feature reviews the medicines available and sets out the pharmaceutical care issues that can improve patient compliance and, therefore, clinical outcomes.

There are two main aspects to the drug treatment of bipolar disorder — the short-term management of acute episodes of mania, hypomania and depression and long-term treatment to maximise the length of time between acute episodes. It is practical to consider the regimens used in acute episodes separately from those used for prophylaxis.

This article presents the currently available evidence for treating bipolar disorder. It is important to be aware that some studies demonstrate the efficacy of off-label or unlicensed indications for drugs or preparations. Pharmacists and prescribers should make sure they know the limitations imposed by marketing authorisations (product licences) for individual products and seek expert advice where appropriate.

### TREATING ACUTE MANIA

Most patients with an acute manic episode will require treatment as a hospital inpatient. In an acute manic episode, the dose of any mood stabiliser should be optimised and treatment with an oral antipsychotic drug or valproic acid be initiated as appropriate. In patients with less severe forms of mania, monotherapy with the existing mood stabiliser may be possible.

For patients not maintained on a mood stabiliser prior to admission, treatment with an oral antipsychotic drug or valproic acid is indicated. Some patients who are acutely unwell may require emergency treatment, following local protocols, with parenteral antipsychotics, benzodiazepines (usually lorazepam) or both. Oral benzodiazepines may also be of benefit in the short-term treatment of acute mania where sedation is a priority, and their use might also reduce the dose of concurrent antipsychotic drugs required. Any drugs that could induce mania, such as antidepressants, should be reduced and discontinued during an acute manic episode. Further information on the categories of drugs available to treat acute mania is set out below:

#### Antipsychotics

Older, “typical” antipsychotic drugs have been used widely and appropriately for the treatment of symptoms associated with acute mania for some time. Although at least one notable review supporting their use exists, there is generally a lack of high quality published evidence about their role.

Parenteral antipsychotics, used according to local protocols, are valuable for emergency situations in particularly agitated patients. Many of the “atypical” antipsychotic drugs have been studied in randomised controlled trials for acute mania. Olanzapine is currently licensed for this indication and the National Institute for Clinical Excellence (NICE) has recently recommended...
that it should be considered as one of the treatment options in acute mania.3 Similarly, quetiapine received a licence for acute mania after publication of the NICE guidance on newer treatments for mania and there is also clinical trial evidence to support its use for this indication.10,11 Risperidone has demonstrated efficacy comparable with that of haloperidol in acute mania12 but it is not as yet licensed in the UK for this indication.

In patients maintained on mood stabilising drugs who develop symptoms of mania, the mood stabiliser dose should be optimised before the antipsychotic drug is added as treatment.

Anticonvulsant drugs Studies have shown valproic acid (mainly as semisodium valproate) to be effective in treating acute mania.13,14 Rapid dose titration is necessary for optimal antimanic effect.

Carbamazepine has also been studied, but it is not licensed for acute mania and is rarely used as a first line treatment.15

Lithium There is limited evidence to support the use of lithium as monotherapy in acute mania, although it may be a feasible option in less severe forms of mania for patients who are maintained on lithium as a prophylactic treatment.16 (See “prophylactic drugs” below for further information about using lithium.)

Benzodiazepines Evidence supports the use of benzodiazepines (usually lorazepam in the UK) as adjunctive treatments, given parenterally if necessary, in patients with mania who are particularly agitated.17

PROPHYLACTIC DRUGS

It is generally advisable to start long-term treatment with mood stabilising drugs in patients who have had just a single severe manic episode. This is because patient outcomes appear to improve if an early relapse is prevented.

The currently preferred strategy is to give continuous (rather than intermittent) maintenance treatment with a mood stabilising agent (with short-term treatments with antipsychotics and benzodiazepines being used at times of acute stress or if early symptoms of relapse are present.)

Lithium is generally considered to be the choice of treatment, with carbamazepine being seen as an alternative, particularly in bipolar II disorder or in patients for whom lithium is ineffective or unacceptable. Further information on these agents and others that are used to prevent relapse is set out below.

Lithium There is systematic review evidence to support the use of lithium as prophylactic treatment in bipolar disorder. For example, short-term and longer-term (up to three years) studies have shown that taking lithium reduces the likelihood of relapse. Lithium has been shown to be effective against both manic and depressive relapse, but is more effective in manic relapse (and is therefore of most use in bipolar I disorder). It has been shown that treating patients who have bipolar disorder with lithium is specifically associated with a reduced risk of suicide. Treatment with lithium should not be suddenly withdrawn because this may lead to the development of mania.20

It should be noted that lithium preparations are not interchangeable — different brands may have widely varying bioavailabilities and so prescriptions should be written for a particular brand, rather than generically. In addition, lithium salts are not equivalent — ie, 200mg lithium carbonate is not equivalent to 200mg lithium citrate. These issues are particularly important, given the narrow therapeutic index of lithium. Patients receiving lithium should be issued with a “lithium card”. Side effects (which are usually dose-dependent) include gastrointestinal disturbance, weight gain, oedema, fine tremor, polyuria (increased frequency of urination), polydipsia (increased thirst) and hypothyroidism. Further information on using lithium clinically (including dosing regimens, monitoring and...
**Panel 2: Summary of key lithium drug interactions**

<table>
<thead>
<tr>
<th>Drugs implicated</th>
<th>Mechanism and effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors/angiotensin-II antagonists</td>
<td>Exact mechanism of interaction unclear; lithium toxicity reported due to increase in lithium levels; renal toxicity may also occur.</td>
</tr>
<tr>
<td>Antacids</td>
<td>Sodium-containing antacids can cause increased lithium excretion leading to decrease in lithium levels and reduced effectiveness.</td>
</tr>
<tr>
<td>Antidepressants — SSRIs, MAOIs</td>
<td>SSRIs — neurotoxicity and increase in lithium levels; lithium toxicity and serotonin syndrome have been reported with certain SSRIs. MAOIs — increase in brain serotonin levels; serotonin syndrome reported with combination.</td>
</tr>
<tr>
<td>Antiepiletics</td>
<td>Carbamazepine — neurotoxicity reported in combination. Phenytoin — limited evidence of lithium toxicity.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>CNS toxicity has been reported with a number of antipsychotics when given in combination with lithium.</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Possible synergistic decrease in calcium ion transport, leading to neurotoxicity, worsening of mania, bradycardia.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Decreased lithium clearance leading to increased lithium concentrations and possible toxicity reported with thiazide (particularly), loop and potassium-sparing diuretics. Acetazolamide has, however, been reported to increase lithium excretion, leading to decreased levels and a loss of efficacy.</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Increased CNS response to lithium leading to increased risk of lithium toxicity/neurotoxicity.</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Increased lithium levels reported with combination; some reports of toxicity.</td>
</tr>
<tr>
<td>NSAIDs/COX-II inhibitors</td>
<td>Decreased lithium clearance leading to increased lithium concentrations and possible toxicity. No such interaction reported with aspirin or sulindac.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Increased lithium clearance leading to reduction in lithium levels and reduced efficacy.</td>
</tr>
</tbody>
</table>

“SSRI” means selective serotonin reuptake inhibitor; “MAOI” means monoamine-oxidase inhibitor; “NSAID” means non-steroidal anti-inflammatory drugs; “COX-II” means cyclo-oxygenase-2 selective and “CNS” means central nervous system. This information is adapted from reference 24.

**SPECIAL POPULATIONS**

In elderly patients, substantially lower doses of psychotropic drugs should be used at all stages in the management of bipolar disorder (see Panel 1 for indications of lithium dose in these patients).

Expert advice should also be sought before prescribing drugs for the treatment of bipolar disorder during pregnancy or lactation — there is a risk of teratogenesis from a number of the drugs used and only limited information is available about their use during breastfeeding (especially for lithium). Patients should be counselled about the “risk benefit” issues.

**CLINICAL GUIDELINES**

There has been recent interest in producing guidelines for the management of bipolar disorder. In 2000 an expert panel in the US produced a consensus guideline, and more recently evidence-based guidelines were developed by the British Association for Psychopharmacology.

The Scottish Intercollegiate Guidelines Network (SIGN) is currently developing guidelines (which are likely to be published later on this year). In addition, NICE is due to publish guidance on bipolar disorder in 2006. This is positive news for health care professionals involved in the care of patients with bipolar disorder and, of course, for patients themselves. This is especially the case because bipolar disorder has been recognised as a condition that has been relatively neglected in the past.

**INDIVIDUAL PATIENT CARE**

One key aspect to individual patient care is teaching patients to recognise the early symptoms of manic relapse and seek early treatment. This is important because it is associated with preventing relapse and improving the social functioning and employment prospects of patients.

Improving compliance is another aspect of individualised care. Compliance issues are particularly associated with the prophylactic use of lithium. Lithium treatment can cause unwanted effects (see above) and patients may see it as bringing a negative influence on their behaviour, personality or lifestyle. Regular three-monthly monitoring of lithium blood concentrations is also required (see Panel 1).

Lithium clinics are useful in improving patient compliance and concordance and therefore clinical outcomes. Community pharmacists also have an important role to play in achieving compliance through monitoring their patients and educating them about the drug. Panel 3 (p143) summarises the pharmaceutical care issues associated with the treatment of patients with bipolar disorder.
### Panel 3: Pharmaceutical care issues in treating patients with bipolar disorder

<table>
<thead>
<tr>
<th>Stage of treatment</th>
<th>Actions</th>
<th>Points to consider</th>
</tr>
</thead>
</table>
| Development of a treatment plan: | Verify the plan in respect of: | - Identifying concomitant physical disorders that are associated with or which complicate the mood disorder  
- Identifying relevant social circumstances, family environment, family stigma and support  
- Alerting the patient to common side effects of medication and provide reassurance  
- Verifying an accurate drug history, including any prior use of antidepressants and other psychoactive agents and over-the-counter (OTC) products  
- Identifying other medication that can cause or aggravate mood disorders  
- Identifying co-morbid states that complicate treatment and its evaluation (e.g., thyroid disorders)  
- Collaborating with other team members to establish alertness to risk of overdose  
- Providing advice on request about patient support groups |
| - Patient comprehension  
- Active participation  
- Patient’s characteristics  
- Indication (the need for each drug)  
- Drug history  
- Choice of medicines  
- Contraindication/interaction  
- Conformity to guidelines  
- Continuity of care | - Patient's characteristics  
- Suitability of medicines  
- Patient's needs for education  
- Concordance and agreed expectations | |
| | Modify the plan to address: | - Specific educational needs  
- Need for individualisation of treatment plan | |
| | Monitor the patient for: | - Including the patient in self-monitoring and good documentation of symptoms where the disease has an irregular course  
- Ensuring dose individualisation using information and preferences from patients  
- Securing support and information from relatives and friends to allow them to supervise medication and report on symptoms when the patient is ill  
- Being similarly alert to the possibility of patients receiving misconceptions about the disease and its treatment from others  
- Checking compliance and maintenance of concordance. Written treatment contracts may support implementation of treatment  
- Checking the handling of medicines and safety of storage  
- Specific monitoring of renal function for lithium in conjunction with therapeutic drug monitoring  
- Watching for specific drug-induced syndromes such as syndrome of inappropriate antidiuretic hormone secretion  
- Checking for specific drug interactions, including those with OTC products | |
| Implementation of the treatment plan: | - Continuing suitability of drug/dose regimen  
- Signs/symptoms of effectiveness and toxicity | |
| - Dose  
- Frequency  
- Timing  
- Compliance  
- Clinical signs  
- Laboratory markers | Adjust the process by: | - Further individualisation in response to monitoring |
| | Confirm evidence of treatment success: | |
| | Prompt a review from: | - Acknowledging adverse effects as perceived by patients  
- Recognising persistent side effects requiring clinical review of the therapeutic plan  
- Confirming adequate duration of acute treatment course  
- Recognising symptomatic changes to allow early referral for a clinical review of the patient's needs |
| - Therapeutic benefit  
- Safety  
- Unwanted symptoms  
- Recorded adverse drug reaction | - Reassure patient in relation to agreed expectations  
- Identification of treatment failure  
- Newly identified patient’s needs  
- Sharing information and discussion of implications with the prescriber and other team members | |
SUMMARY

Progress in treating patients with bipolar disorder continues to be made. Relatively recent developments include the use of atypical antipsychotic drugs to control manic episodes and as maintenance therapy.

In addition, SIGN guidelines are expected at the end of the year and NICE guidelines are due out in 2006. These developments will be particularly welcome given that bipolar illness has been a relatively neglected condition to date. A greater understanding of the neurobiology involved should further aid the development of new drugs.

REFERENCES


This list of references is abridged. A full list is available on the next page.
REFERENCES


