Pharmacological treatment of bipolar disorder

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What's new?

- There is growing evidence for the use of atypical antipsychotics, not only in acute treatment of manic and mixed relapses but also in maintenance therapy, with guidelines now advocating olanzapine as a first-line therapy in long-term management

Abstract

Bipolar affective disorder, classically characterized by repeated episodes of mania interspersed with periods of depression, is a serious mental illness associated with significant morbidity and mortality. Management is aimed at both the rapid treatment of acute episodes and long-term prophylaxis. There continues to be a lack of good-quality research available on which to base treatment regimens, particularly with regard to long-term management, rapid cycling, optimal treatment of bipolar depression and the use of antidepressants, and in the efficacy and safety of drug combinations. Lithium continues to be advocated as a first-line treatment, particularly in long-term therapy. Over recent years the anticonvulsant valproate has joined lithium as an alternative first-line therapy, despite what some would argue as a relative dearth in conclusive evidence. There is also growing evidence for the use of lamotrigine and atypical antipsychotics, particularly olanzapine, not only in the treatment of acute manic and mixed relapses but also as prophylactic therapy. Management of bipolar affective disorder needs to be tailored to the individual, with psychoeducation, psychological and social interventions included in a comprehensive package of care, along with pharmacological treatments.

Keywords acute treatment; anticonvulsants; antidepressants; antipsychotics; bipolar affective disorder; lithium; long-term treatment

Bipolar affective disorder is classically characterized by intermittent recurrent episodes of mania (Type I) or hypomania (Type II) interspersed with episodes of depression. Most patients have a recurrent illness, with many experiencing persistent subsyndromal symptoms (especially those of depression) between episodes. There is a significant impact on quality of life, with poor occupational, leisure and social functioning. Management is aimed at both rapid treatment of episodes, and in the long term at preventing or reducing the frequency and severity of episodes and in ameliorating chronic symptoms and their impact. There are numerous drugs available for both the acute and long-term treatment of bipolar disorder, with many having efficacy in both. Several factors need to be considered when planning treatment (see Table 1) and each management plan needs to be tailored to the individual, providing support and education for patients and their carers, along with psychological and social interventions.

Lithium

Utilized in the treatment of bipolar disorder for over 50 years, lithium has efficacy in both the acute and prophylactic treatment of bipolar disorder. It has many molecular targets but it is not yet known which are necessary for its therapeutic effect. Lithium reduces neuronal excitability by modulating action-dependent sodium channels and excitatory neurotransmission, and also affects second-messenger systems, and may have neuroprotective or even neurotrophic effects.[1]

It has an anti-manic effect and can be used as monotherapy for the acute treatment of less severe manic or mixed episodes,[2,3] particularly if symptoms have responded to lithium previously (Table 2). However, other medications, particularly antipsychotics, may be better, especially if symptoms are severe, associated

Factors influencing choice of medication in bipolar disorder

- Phase of the illness – acute episode or prophylaxis
- Symptom profile (including severity) or subtype of the condition – bipolar I or II, mixed episode (where manic and depressive feature co-exist) or depressive episode
- Presence of rapid cycling (the occurrence of at least four episodes of illness in the preceding 12 months)
- Prior response and tolerability (including family history of drug response)
- Current medication
- Medical and psychiatric comorbidity
- Side effects
- Drug interactions
- Special considerations such as pregnancy or lactation
- Patient preferences

Table 1

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Summary of treatment recommendations

Acute mania or mixed episode and not on long-term treatment	Severe: antipsychotic (e.g. olanzapine, quetiapine or risperidone) or valproate Less severe: also consider lithium or carbamazepine If mood incongruent psychotic symptoms present, use an antipsychotic Stop antidepressants abruptly or gradually, depending on clinical context If symptoms remain inadequately controlled despite the above: consider combination therapy (e.g. lithium or valproate with an antipsychotic) consider clozapine in more refractory illness
Acute mania or mixed episode whilst on long-term treatment	Optimize current treatment, check plasma levels and increase dose if appropriate If this is inadequate, consider adding an antipsychotic to lithium or valproate, or vice versa
Acute bipolar depression and not on long-term treatment	Severe: antidepressant (SSRI) and an anti-manic agent (lithium, valproate or an antipsychotic; the latter particularly if the patient has psychotic symptoms) Less severe: consider lithium, lamotrigine or valproate
Acute bipolar depression whilst on long-term treatment	Optimize current treatment; if limited response, initiate an antidepressant (if already on one, consider augmentation or change to another)
Rapid cycling	Stop antidepressants Consider lithium, valproate or lamotrigine Combination treatment may well be indicated (e.g. lithium and valproate)
Maintenance	Lithium, olanzapine or valproate Combinations of two of the above (and possibly with the addition of an antidepressant) may be indicated if suboptimal control; if this remains ineffective consider lamotrigine or carbamazepine Consider clozapine in treatment-resistant patients

Table 2

with mood-incongruent psychotic symptoms or if there is significantly disturbed behaviour. Lithium can also be used in combination with an antipsychotic or valproate if symptoms are inadequately controlled or are particularly severe. In the treatment of an acute depressive episode it can be used in combination with an antidepressant or alone if symptoms are less severe, although evidence for its efficacy in the latter is limited.[2]

There is strong evidence to support the use of lithium in bipolar prophylaxis, where it reduces both the number and severity of relapses, and guidelines continue to advocate it as one of the first-line monotherapies.[2,3] It is effective against both manic and depressive episodes, but appears to have a greater efficacy in the prevention of mania.[4] A Cochrane review suggested that the number needed to treat (NNT) for 1 year in order to avoid one relapse ranged from 4 to 14.[4] There is also evidence that long-term treatment is associated with a significant reduction in suicide rates.[5]

Before prescribing lithium, baseline measures of renal, thyroid and cardiac function, as well as a pregnancy test for women of childbearing potential (because of the potential teratogenic effects of lithium: neural tube, craniofacial and cardiac anomalies) should be carried out. The medication is usually given as a single dose at night, starting at 400 mg/day, and the aim is to achieve a blood level of around 0.5–1.0 mmol/l. The levels should be checked when the drug has reached steady state in the plasma (about 5 days after any change of dose) and, once stable, should be checked every 3–6 months. The highest dose tolerated within this range is the optimal maintenance dose, which is usually between 600 and 1200 mg/day, although doses should be lower when renal function is compromised.

Common side effects of lithium include gastrointestinal disturbance, tremor, polyuria, polydypsia, sedation, lethargy and weight gain. Uncommon but potentially serious side effects of prolonged administration include impairment in renal and thyroid function and hyperparathyroidism. These are reversible on early discontinuation but require regular (6-monthly) monitoring for early detection. Lithium has a very narrow therapeutic range, with toxicity usually occurring when plasma levels rise above 1.5 mmol/l. Toxicity is potentially life-threatening and usually presents with gastrointestinal and CNS effects, which can progress to coma and death. It requires urgent hospitalization, and sometimes haemodialysis. A disadvantage of lithium is that abrupt discontinuation may trigger acute episodes; gradual withdrawal over at least 1 month is therefore advocated.

Anticonvulsants

Valproate

Valproate is available as sodium valproate, semisodium valproate and valproic acid. It inhibits neuronal sodium channels and glutamate release and, like lithium, acts on second-messenger systems and induces the expression of neuroprotective genes and proteins. It is now advocated as a first-line monotherapy in the treatment of acute mania[6] and mixed episodes (where it may be superior to other agents),[2,7] especially if symptoms have responded before,[3] and as a maintenance treatment in reducing

both depressive and manic relapses.[2,3,7] There is evidence that it can be helpful in rapid cycling both as an initial treatment and in the long term when used in combination with lithium or lamotrigine, if initial management strategies fail.[2,3] It appears to have limited efficacy as a monotherapy in depression but may protect against antidepressant-induced mania in those requiring antidepressant treatment for an acute depressive episode.

Renal and hepatic function, as well as a full blood count, need to be checked before starting treatment and then at 6-monthly intervals.[7] Plasma level monitoring may be of limited use as there is no clear relationship between plasma levels and efficacy or side effects, although recommended levels are around 50–125 μg/ml. The starting dose is between 500–750 mg/day, increasing to about 2500 mg/day depending on response and tolerability. Common side effects include gastrointestinal problems, weight gain, sedation and hair loss. Rarely, it can cause thrombocytopenia and platelet dysfunction (usually benign), ataxia, pancreatitis and liver toxicity.[7] Valproate also has complex interactions with other medications. It has been suggested that it should not be used routinely in women of childbearing age and it is important that women are aware of its teratogenic effects (neural tube defects, valproate foetal syndrome), and the possibility that it may cause polycystic ovaries or hyperandrogenism.[3]

Lamotrigine

Lamotrigine is an anticonvulsant and was the first agent to be approved specifically for maintenance treatment of bipolar depression, though it is currently not advocated as a first-line therapy. It has some efficacy both as an acute treatment for less severe bipolar depression[2,3] and possibly in the acute treatment of mania. Lamotrigine may also be used in prophylaxis, alone or in combination with lithium or valproate,[3] when first-line therapies have failed, particularly where the burden is depressive or in bipolar II,[3] and in the treatment of rapid cycling.[2]

Side effects include headache, ataxia, diplopia and vomiting. There is also a risk of exfoliating dermatitis, which may be fatal if allowed to progress to Stevens–Johnson syndrome or toxic epidermal necrolysis, and it is therefore important to monitor for any new rash. The risk is increased if the dose is started too high or increased too quickly, or when given together with valproate. The risk can be significantly reduced, to about 0.1%, if the drug is titrated slowly. The usual regimen is 25 mg/day for 2 weeks, increasing to 50 mg/day for another 2 weeks. Increments of 50 mg can then be added, to a maximum of 400 mg/day. If a rash appears, which is usually within 8 weeks of starting therapy, the medication should be stopped immediately. It can be reintroduced at a slower titration regimen except in severe cases. Valproate increases the level of lamotrigine by inhibiting its hepatic metabolism, so if used in combination the starting dose of lamotrigine should be halved.

Carbamazepine

Carbamazepine is not advocated as a first-line therapy in recent guidelines[2] but may have some efficacy either alone or in combination with other medications[8] in treatment-resistant cases. Evidence indicates that it is less effective than lithium[2] and its clinical usefulness is limited by significant problems with tolerability and interactions with other drugs, the latter because of changes in liver metabolism and protein binding. Up to 50% of patients treated with carbamazepine experience side effects such as nausea, fatigue, ataxia, blurred vision and diplopia, whilst rare but potentially fatal adverse effects include agranulocytosis, aplastic anaemia, liver failure, pancreatitis and exfoliative dermatitis. Haematological and hepatic screening and regular monitoring are recommended before initiation and during treatment. Carbamazepine can be fatal in overdose, and manifestations of toxicity include a variety of CNS, respiratory and cardiac symptoms. As it induces liver metabolism it decreases the plasma levels of many medications, including other anticonvulsants, antipsychotics, benzodiazepines, tricyclic antidepressants and contraceptives. Other drugs that inhibit its metabolism (e.g. selective serotonin reuptake inhibitors (SSRIs)) can lead to increased plasma levels. Oxcarbamazepine, a related compound with better tolerability, is sometimes used as an alternative to carbamazepine.

Antipsychotics

Atypical antipsychotics

These have efficacy in the acute treatment of mania and mixed episodes and are advocated as first-line monotherapy (olanzapine, risperidone, quetiapine and aripiprazole), especially if symptoms are severe or are associated with disturbed behaviour.[2,3,9] They can also be used as an adjunct if a patient experiences a relapse whilst already on another class of medication.[2] Olanzapine in particular has been shown to be as least as effective as lithium or valproate.[10] There is limited evidence for their use in bipolar depression (e.g. quetiapine), mainly when used in combination with an antidepressant.[9] There is increasing evidence for their efficacy in prophylaxis, although they may be more effective in preventing manic and mixed episodes, with most data currently available for olanzapine.[9,10] National Institute for Health and Clinical Excellence (NICE) guidelines suggest olanzapine as a first-line therapy in long-term management and in combination with another drug if treatment proves refractory. Their main disadvantage is their propensity to produce metabolic side effects such as increased blood levels of glucose and lipids, and weight gain. Clozapine is effective in the treatment of patients who have responded poorly to, or are unable to tolerate, other medications. Its use is limited, however, by requirements for regular blood monitoring to avoid agranulocytosis.

Typical antipsychotics: the use of typical antipsychotics has diminished in recent years with the advent of the atypicals. They have efficacy in acute mania but there is limited evidence for their use in other aspects of treatment.

Antidepressants

Antidepressants can be used in combination with an anti-manic agent (lithium, valproate or an antipsychotic) for the treatment of both acute depressive episodes and in long-term therapy for those who suffer from recurrent episodes. Monotherapy is generally not recommended as there is evidence that there is a risk of switching to mania. Tricyclic antidepressants may have a greater risk of this and are generally used only in treatment resistance. Most guidelines recommend discontinuation of antidepressants on the onset of a manic episode,[2,3] or when there is rapid cycling,[2] though there are alternative views.[11]

Conclusion

Despite the availability of numerous medications in the management of bipolar disorder there continues to be a lack of good-quality research on which to base treatment regimens. No drug has yet been found to be equally as effective in controlling manic and depressive relapses, whilst many patients remain only partially responsive to treatment, even with combination therapy. It is important to tailor treatment to the individual's complex needs, with pharmacological management being only a part of the comprehensive and holistic treatment plan. ◆

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