Acute and long-term treatment of mania

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The treatment of mania starts with a correct diagnosis and elementary measures to prevent risks for the patient, relatives, and others. Sometimes, compulsory admission and treatment may be required for a few days. Patients with psychotic or mixed mania may be more difficult to treat. At the present time, there is solid evidence supporting the use of lithium, the anticonvulsants valproate and carbamazepine, and the antipsychotics chlorpromazine, haloperidol, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and asenapine in acute mania, and some evidence supporting the use of clozapine or electroconvulsive therapy in treatment-refractory cases. However, in clinical practice, combination therapy is the rule rather than the exception. The treatment of acute mania deserves a long-term view, and the evidence base for some treatments may be stronger than for others. When taking decisions about treatment, tolerability should also be a major concern, as differences in safety and tolerability may exceed differences in efficacy for most compounds. Psychoeducation of patients and caregivers is a powerful tool that should be used in combination with medication for optimal long-term outcome. Functional recovery should be the ultimate goal.

M anic-depressive illness, currently known as bipolar disorder, is a common, severe, long-term condition. The World Health Organization reported in 2001 that bipolar disorder was the fifth cause of life years lived with a disability among young adults. It is characterized by the recurrence of mania, depression, or mixed episodes. Mania is the most characteristic phase of bipolar disorder, and a major cause of disability, stigma, and cognitive impairment. Lithium is the traditional treatment option, but the majority of patients do not respond to lithium monotherapy, and other drugs have been introduced in the past decades, such as the anticonvulsants valproate and carbamazepine. Other newer anticonvulsants, which have failed to prove their efficacy in mania, have not been used successfully. Antipsychotics are established as the main treatment for schizophrenia, and have been traditionally used in mania, but recently a growing number of trials have turned them into a broader therapeutic option for bipolar disorder, as both alternative and adjunct to traditional mood stabilizers. Second-generation antipsychotics have been extensively studied in mania, but there is also increasing evidence of the efficacy of at least some of them in the treatment of bipolar depression and maintenance treatment of bipolar disorder. Moreover, secondary analysis from controlled trials suggest that some antipsychotics may be helpful in the treatment of mixed episodes.

Keywords: mania; lithium; anticonvulsants; antipsychotics; clinical trials; bipolar disorder

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In clinical reality, as demonstrated in large naturalistic studies, the majority of patients with acute mania are treated with combinations of the drugs mentioned above, and even benzodiazepines as adjuvant treatment.\(^8\) As an alternative option to lithium, anticonvulsants, and antipsychotics, or their combination, electroconvulsive therapy is supported mainly by experience and some limited evidence.\(^9,10\) The treatment of milder forms of mania and hypomania has clearly been insufficiently studied, although it is generally assumed that what works for mania should work for hypomania as well; however, clinical decisions are generally made on a benefit:risk ratio framework, and therefore more head-to-head studies and specific trials in this subpopulation are needed. Psychotic mania has been better studied, and most trial reports provide separate analysis for psychotic versus nonpsychotic patients. Finally, mixed mania has also been studied in some trials, and may respond better to valproate, atypical antipsychotics—or a combination of the two—than to other traditional therapies.\(^11\) but still remains a challenge, especially due to the high risk of switch to depression.\(^12\)

### Management of acute mania: first steps

The goals of treatment of an acute manic or mixed episode are to alleviate symptoms and allow a return to usual levels of psychosocial functioning. Achieving rapid control of agitation, aggression, and impulsivity is particularly important to ensure the safety of patients and those around them, and to allow the establishment of a therapeutic alliance. Sometimes, compulsory hospitalization is needed to start effective treatment. Although diagnostic criteria allow bipolar mood episodes to be defined as hypomanic, manic, or mixed, it can be difficult to reliably discriminate between them. The degree or mood elevation per se is not the decisive factor in choosing among the three diagnoses; instead, the degree of impairment and behavioral disturbance, as evidenced by aggression, agitation, psychosis, poor judgment, and social or occupational dysfunction, is the usual precipitant of clinical attention and hence the primary target of intervention. In practical terms, therefore, bipolar I patients presenting with a hypomanic, manic, or mixed episode can usually be managed with a common “acute mood elevation” strategy. However, even if the split between acute treatment and long-term treatment makes sense from an operational perspective, in the last few years it has come clear that the best approach to the treatment of bipolar disorder is an integrative management approach, dealing with the urgent and acute issues while keeping perspective on the long-term ones and functional outcome.}

The treatment of mania must always take into account the long-term issues, including not only the cross-sectional assessment but also the predominant polarity of episodes,\(^13\) and the general principles as specified in the decalogue for the management of bipolar disorder,\(^14\) shown in Table I.

### Pharmacological treatment of acute mania

The most widely used medications in the acute setting are lithium, some anticonvulsants (valproate, carbamazepine), standard antipsychotics (eg, haloperidol, chlorpromazine), atypical antipsychotics (eg, quetiapine, olanzapine, risperidone, ziprasidone, aripiprazole, clozapine), and benzodiazepines (eg, lorazepam, clonazepam). The choice of initial treatment is influenced by the patient’s current and prior medication history, the need for rapid resolution of agitation and aggression, the characteristics of the manic episode, and the presence of rapid cycling, as well as the patient’s own willingness to accept particular therapies and routes of administration. Whenever possible, oral therapy should be offered first, but intramuscular injections are an alternative if oral therapy cannot be reliably administered. The published consensus, clinical guidelines, and treatment algorithms show some differences in their recommendations for the first- and second-line treatment of

| 1. To ensure the safety of the patient and others |
| 2. To treat and reduce the severity of acute mood episodes when they occur |
| 3. To treat psychotic symptoms when they occur |
| 4. To avoid cycling from one episode to another |
| 5. To prevent suicidal behavior |
| 6. To reduce the frequency of mood episodes |
| 7. To treat subthreshold symptoms |
| 8. To treat comorbidities, overall health, and cognitive problems |
| 9. To increase the patients’ and caregivers’ knowledge about the disorder and enhance treatment adherence |
| 10. To help the patient function as effectively as possible between episodes |

Table I. The decalogue of goals for intervention in bipolar disorder.\(^14\)
acute mania. Although the majority support the use of monotherapy with lithium, valproate, and in some cases olanzapine and other antipsychotics in mild-to-moderate mania, there is increasing recognition that a significant number of patients will end up receiving two or more drugs.

**Lithium**

Lithium has been used in the treatment of acute bipolar mania for over 50 years, and has demonstrated superiority over placebo in several controlled clinical trials. In these studies, the percentage of patients showing at least moderate improvement after 2 to 3 weeks of treatment ranged from 40% to 80%. Lithium appears to be most effective in patients with classic (euphoric) mania, while response rates are relatively poor in mixed states or rapid cycling. Drawbacks of lithium therapy include its narrow therapeutic index (recommended plasma level 0.8 to 1.2 mmol/L), poor tolerability, especially at higher doses, and risk of “rebound mania” on withdrawal. Common side effects of lithium are tremor, polydipsia, polyuria, and, in the long term, hypothyroidism. Despite these shortcomings, lithium retains a role as a first-line treatment and is widely seen as the gold-standard comparator for newer agents, not to say that it may have antisuicidal effects. Lithium also been evaluated in relation to other antimanic agents. Head-to-head comparisons with antipsychotic drugs (usually chlorpromazine) have generally found lithium to be superior in terms of overall improvement in symptoms, mood, and ideation, but worse with respect to motor hyperactivity and onset of action. Lithium was as efficacious as quetiapine in a 12-week, randomized, double-blind trial. In a three-arm randomized study comparing placebo, lithium, and valproate, lithium and valproate were similarly effective in improving manic symptoms. Randomized comparisons of a mood stabilizer (lithium or valproate), alone or in combination with antipsychotics, generally found that the combinations were superior to monotherapy for the rapid control of manic symptoms. By contrast, two double-blind studies failed to show superiority of lithium plus an antipsychotic (haloperidol or pimozide) over the antipsychotic alone in the treatment of acute mania. Lithium has also been found to be well tolerated in combination with either antipsychotics or anticonvulsants.

**Anticonvulsants**

**Valproate**

Several galenic forms of valproic acid, the final active product, are available across the world, and have been used since the 1960s in Europe for the treatment of bipolar disorder. Subsequently, two double-blind studies found valproate to be superior to placebo and as effective as lithium in the treatment of acute mania. A pooled analysis of these studies indicated that 54% of patients treated with valproate experienced a reduction of at least 50% in manic symptomatology. Unlike lithium, valproate has a rapid onset of action, producing significant clinical improvements within 1 week, and is equally effective in treating mixed and classic mania. Valproate may not be as efficacious as antipsychotics such as olanzapine, but is generally better tolerated. An extended-release form of valproate is also available and proven to be effective in mania. Some guidelines, such as the United Kingdom NICE guidelines, advise against the use of valproate in women of childbearing age, due to the high frequency of unplanned pregnancies in women with and even without bipolar disorder, and the relatively high teratogenicity of the compound, but this may be going too far, and could prove impractical. Other potential acute side effects of valproate are weight gain and hair loss.

**Carbamazepine**

Since its introduction into psychiatric treatment, carbamazepine has been evaluated in several randomized controlled trials, but most had methodological limitations such as small patient numbers or concomitant treatment. A placebo-controlled study in which patients were not receiving adjunctive medication found that 63% of carbamazepine-treated patients displayed significant improvements in manic, depressive, and psychotic symptoms, an effect that was lost on switching to placebo. The statistical significance of the treatment effect was not given, however. Recently, two randomized, double-blind studies have assessed an extended-release formulation of carbamazepine as monotherapy for the acute treatment of manic or mixed episodes. Both trials found carbamazepine to be significantly superior to placebo; side effects included dizziness, somnolence, nausea, vomiting,
ataxia, blurred vision, dyspepsia, dry mouth, pruritus, and speech disorder.

Two studies have compared carbamazepine with lithium in a randomized, controlled manner, with conflicting results. One found that lithium was superior, while the other found the drugs to be equivalent. Two studies comparing carbamazepine with chlorpromazine have found no differences between the drugs. A double-blind study found that carbamazepine in combination with lithium was as effective as lithium plus haloperidol in the treatment of acute mania. In all these studies, the antimanic effect of carbamazepine became evident after 1 to 2 weeks.

Uncontrolled studies have suggested a role for carbamazepine in rapid cycling and mixed states, but these require confirmation. A potentially life-threatening side effect of carbamazepine may be the Stevens-Johnson syndrome and related dermatologic effects.

Other anticonvulsants

Newer anticonvulsants such as lamotrigine, gabapentin, and topiramate have failed to demonstrate superiority over placebo in randomized controlled studies of bipolar mania, and there is practically no evidence to support the use of tiagabine, levetiracetam, pregabalin, or zonisamide. There is some limited evidence that phenytoin may possess antimanic effects. Oxcarbazepine, structurally similar to carbamazepine, may possess antimanic effects, but licarbazepine, its main active metabolite, failed in at least one placebo-controlled trial. Clearly, not all anticonvulsants are antimanic.

Antipsychotics

Antipsychotics have been used since their introduction in clinical practice for the treatment of acute mania. For years, though, the evidence base for this practice was extremely limited. Now, the US Food and Drug Administration (FDA) has already approved six antipsychotics for the treatment of acute mania: chlorpromazine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Current criteria for FDA approval include two multicenter, randomized, double-blind, placebo-controlled trials with adequate sample sizes supporting the safety and efficacy of these agents. These drugs are also approved for the treatment of mania in most European countries and in most countries worldwide.

Chlorpromazine

Chlorpromazine is a first-generation antipsychotic that has been studied only in one small, placebo-controlled trial and a few comparative, randomized studies, versus lithium, haloperidol, and pimozide. The main problems related to chlorpromazine use are extrapyramidal symptoms, tardive dyskinesia (long-term), and hepatotoxicity.

Haloperidol

Only recently have the results of placebo-controlled trials with this drug become available. Studies conducted in the 1970s already suggested that it could be efficacious in mania, and recent trials have shown that it has strong antimanic properties, but it may also carry important side effects such as extrapyramidal symptoms and tardive dyskinesia, among others. It is particularly relevant to mention that, although haloperidol seemed to have a faster onset of antimanic action than other antipsychotics in several controlled trials, it also significantly reduced the time until first depressive recurrence in one of them. Haloperidol has been compared as monotherapy with placebo, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and as an add-on to placebo and risperidone.

Clozapine

Clozapine is the prototype of an atypical antipsychotic, but has not been as widely studied as the others in its class, due to the risks of seizures and agranulocytosis. Thus, to date we have no double-blind clinical trials on clozapine in acute mania. Nevertheless, there are open studies with a few patients showing that clozapine could be effective as a treatment for dysphoric mania. Twenty-seven patients with acute mania were recruited for an open study in which they were divided into two groups: 15 would take clozapine, the remaining 12 taking chlorpromazine. The clozapine-treated group achieved significantly greater reduction in Young Mania Rating Scale (YMRS) scores at the second week but not at the third week, this suggesting a probably faster improvement of mania through clozapine treatment. A prospective trial was set for 25 acutely manic patients with either bipolar disorder (n=10) or schizoaffective disorder-bipolar subtype (n=15) First-line treatments (lithium, anticonvulsants) and antipsychotics were not
effective, produced intolerable side effects, or both. Seventy-two percent improved on the YMRS and 32% improved on the Brief Psychiatric Rating Scale (BPRS). Bipolar and nonrapid cycling patients had significantly greater improvement as compared with schizoaffective patients and rapid cyclers respectively. According to this trial, clozapine could be an effective therapy for treatment-resistant bipolar and schizoaffective mania.55 Besides the potential risk for agranulocytosis and seizures, other potential side effects of acute use of clozapine include clinically significant weight gain and sialorrhea.

Risperidone

There are several studies on the antimanic effect of risperidone as monotherapy. A 3-week, multicenter, double-blind, placebo controlled trial was carried out recently in 259 patients.56 Risperidone significantly improved both YMRS and CGI (Clinical Global Impression). Improvement was significant from the third day of treatment onwards ($P<0.01$ vs placebo). Another 3-week trial recruited 290 bipolar I patients: those randomized to risperidone improved significantly from the third day compared with placebo, and made quicker breakthroughs than those randomized to placebo. Response to treatment was defined as at least 50% decrease in YMRS score: it was achieved in 73% and 36% of those randomized to risperidone and placebo respectively ($P<0.001$). The main downsides of risperidone were the risk of dose-related extrapyramidal symptoms and hyperprolactinemia.57 Smulevich et al designed a 3-week controlled trial in which manic patients would receive risperidone, haloperidol, or placebo followed by a double-blind trial of risperidone and haloperidol. The conclusion was that risperidone and haloperidol were similarly effective in the treatment of acute mania, this being significant compared with placebo. Risperidone was reported to be safer, and efficacy was maintained over the long term.46 Risperidone has also been studied as adjunct treatment to lithium, valproate semisodium, or carbamazepine. A 3-week, double-blind, randomized, controlled trial studied mood stabilizers plus risperidone or placebo in the treatment of acute mania. The study end point YMRS scores improved by −14.5 and −10.3 in the risperidone and placebo groups respectively, not reaching statistical significance ($P<0.089$), probably because of the effect of carbamazepine on risperidone’s plasmatic levels through hepatic enzyme induction. When risperidone plus lithium or valproate semisodium were compared with placebo plus lithium or valproate semisodium, YMRS scores improved by −15.2 and −9.8, this being statistically significant ($P<0.047$) In another trial a double-blind, placebo-controlled comparison was made between haloperidol, risperidone, or placebo added to a mood stabilizer in patients with acute mania.46 Both haloperidol and risperidone achieved significantly greater reductions in YMRS scores than the placebo group. It should be noted that, despite the titles of the articles, both studies included patients with mixed states.

Some authors suggested that risperidone could exacerbate or induce mania, presumably through antidepressant effects but further trials confirmed that risk to be very low.

Olanzapine

Olanzapine is the most studied of all the atypical antipsychotics.63 It has been studied as monotherapy treatment for acute mania with positive results in several trials. Two randomized, double-blind, placebo-controlled trials were carried out: over 3 or 4 weeks, patients received placebo or olanzapine. Response was again defined as at least 50% improvement on YMRS score. In the first trial 48.6% of the olanzapine group and 24.2% of the placebo group responded. In the second trial the percentages increased to 64.8% and 42.9%. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania was published in 2003.48 Olanzapine failed to best haloperidol in improving manic symptoms, but patients randomized to haloperidol switched more rapidly to depression. Olanzapine has also been compared with lithium and divalproex in the treatment of mania. In a 4-week double-blind trial, manic patients were randomized to olanzapine or lithium. Olanzapine was at least as effective as lithium.66 A 3-week, randomized, double-blind trial compared olanzapine with divalproex for the treatment of manic or mixed episodes. Olanzapine-treated patients had a higher decrease in YMRS scores than divalproex-treated ones. Percentages of response (reduction of at least 50% of the YMRS score) were 54.4% and 42.3%, respectively. Dry mouth, weight gain, increased appetite, and somnolence were more reported amongst the olanzapine patients, while nausea was more frequent in the
Pharmacological aspects

Divalproex group. A randomized 12-week, double-blind multicenter study compared both drugs, finding no significant difference in efficacy between treatment groups. Divalproex was associated with fewer adverse events (including weight gain) than olanzapine. A 6-week double-blind, randomized, placebo-controlled trial was developed in order to compare combinations of olanzapine plus lithium or valproate vs lithium or valproate alone. The patients included suffered from an acute manic or mixed bipolar episode, and were inadequate responders after 2 weeks of mood stabilizer alone. Rates of improvement on YMRS scores were significantly higher with combined treatment (67.7% vs 44.7%; P<0.001). Improvement itself was higher too (-13.11 vs -9.10; P=0.003). Those patients with mixed episodes presenting moderate-to-severe depressive symptoms (DSM-IV criteria for mixed episode; Hamilton Rating Scale for Depression [HAMD] at least 20 at baseline), olanzapine cotherapy improved HAMD scores to a greater extent (10.31 points compared with 1.57 for mood stabilizer alone; P<0.001). A recent trial failed to prove any further benefit of the addition of olanzapine to carbamazepine as opposed to carbamazepine alone. One of the major drawbacks of olanzapine is its weight gain liability, and some tendency to increase glucose and lipid levels in blood in the longer term.

Quetiapine

Three hundred and two patients with an acute manic episode participated in a double-blind trial being randomized to quetiapine, haloperidol, or placebo. At day 21 quetiapine had improved YMRS score (-12.29 vs -8.32 for placebo; P<0.01) At day 84 difference from placebo was also significant (-17.52 vs -9.48; P<0.001). At day 21 haloperidol-treated patients were significantly improved (-15.71; P<0.001) as well as at Day 84 (-18.92; P<0.001). Quetiapine, lithium, and placebo were randomly administered to manic patients in a double-blind trial. This second-generation antipsychotic was significantly superior to placebo in reducing YMRS score and similar to lithium. A combined analysis of these two trials supported quetiapine as fast-acting and well tolerated in the treatment of mania. Somnolence and hypotension were the main adverse events, which also included some weight gain. Two randomized, double-blind, placebo-controlled studies were designed to evaluate the efficacy and tolerability of quetiapine when adjunctioned to lithium or divalproex in the treatment of acute mania. In one of them, the quetiapine-mood stabilizer group had a significantly greater reduction in the YMRS score when compared with the placebo-mood stabilizer group (-13.76 vs -9.93; P=0.021). The response rate (reduction of at least 50% of the YMRS score) was significantly higher in the quetiapine-mood stabilizer group than in the placebo-mood stabilizer group (54.3% vs 32.6%; P=0.005) Clinical remission (YMRS score below 12) was also significantly higher (45.7% vs 25.8%; P=0.007). In the second study, quetiapine did not separate from placebo at study end point. One of the commonest side effects of quetiapine is sedation.

Ziprasidone

A 3-week double-blind trial randomized 210 patients with a manic or mixed episode either to ziprasidone or to placebo. The study evaluated the efficacy and tolerability of ziprasidone compared with placebo. Patients on ziprasidone improved relative to baseline and placebo on all primary and most secondary efficacy measures at end point. Measures included were Clinical Global Impression (CGI, severity and improvement), Positive and Negative Syndrome Scale (PANSS), and Schedule for Affective Disorders and Schizophrenia-Change Mania Rating Scale (SADS-C MRS). Responders to treatment (at least 50% improvement on MRS) were 50% of the ziprasidone group and 35% of the placebo group (P<0.05). Another 3-week trial was newly positive for ziprasidone. Somnolence and extrapyramidal symptoms were the most reported adverse events. A third monotherapy placebo-controlled trial also had a haloperidol arm, and showed significant superiority over placebo but lower efficacy versus haloperidol (up to 30 mg/day) at the 3-week and 12-week end points. Two hundred and five bipolar patients receiving lithium were part of a double-blind trial that studied ziprasidone as add-on treatment over 3 weeks. This trial failed to yield positive results. Somnolence, extrapyramidal symptoms, dizziness, and agitation were more frequent in the group receiving ziprasidone and lithium. Another potential side effect of the drug is activation (some sort of akathisia vs anxiety and restlessness). Further add-on controlled trials are currently ongoing with ziprasidone.

Aripiprazole

Aripiprazole is a partial agonist of dopamine D2/D3 and serotonin (5-HT)1A receptors and an antagonist of
5-HT₂A and histamine H₁ receptors, and a moderate serotonin reuptake inhibitor. This agent demonstrated a superior response rate to haloperidol (50% vs 28.4%) in patients remaining on treatment in a 12-week comparative trial. Two hundred and sixty-two patients with an acute manic or mixed episode were randomized either to aripiprazole or placebo. They were hospitalized at least for 2 weeks and followed for an extra week. Aripiprazole significantly improved YMRS scores (-8.2 vs -3.4 for placebo; \( P<0.01 \)) Response rate was significantly higher too (40% versus 19%; \( P<0.01 \)) The percentage of aripiprazole-treated patients achieving response was significantly higher than that of placebo-treated patients as early as day 4 (14% vs 5%; \( P<0.05 \)) This was confirmed by a second 3-week study. Akathisia was significantly higher with aripiprazole when compared with placebo. Another trial randomized manic patients to aripiprazole (n=175) or haloperidol (n=172). After 12 weeks, 50.9% of aripiprazole-treated patients and 29.1% of the haloperidol group responded to treatment. Greater tolerability for aripiprazole should be considered when discussing these data, because the definition of response included the capacity to stay in the trial until its end. There is only one very recent placebo-controlled trial with aripiprazole as adjunctive treatment of mood stabilizers, which showed better efficacy for the combination. Activation and akathisia have been reported with aripiprazole.

Amisulpride

Only one controlled trial is available for this drug in mania. A multicenter, open, randomized trial compared amisulpride with haloperidol in manic patients taking valproate. Amisulpride was not significantly superior to haloperidol, but was better tolerated. In Spain, an open, prospective, 6-week study was carried out with 20 patients with an acute manic episode (YMRS score of 20 or more) YMRS, the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions Scale for Bipolar Disorder, Modified (CGI-BP-M) and the systematic report of adverse events were used to evaluate results. No other antipsychotics were used. Seventy percent completed the study. Amisulpride significantly improved the YMRS (\( P=0.0001 \)), the HAM-D (\( P=0.0141 \)) and the overall (\( P=0.0003 \)), mania (\( P=0.0001 \)) and depression (\( P=0.0268 \)) subscales of the CGI-BP-M. Researchers conclude that despite design limitations (open, observational, small size) their prospective study suggests that amisulpride could be an effective and reasonably safe treatment for acute mania. Amisulpride may carry some risk of extrapyramidal side effects and hyperprolactinemia.

Zotepine

A group from Germany has recently reported an open study with zotepine. Zotepine blocks D₁, D₂, 5-HT₁, and 5-HT₂ receptors. It behaves as a noradrenaline reuptake inhibitor and antagonizes muscarine acetylcholine (mAch) and H₁ receptors, being sedative. Thus, its profile is that of an atypical antipsychotic. Twelve patients with severe manic episodes (mean YMRS 45+-7) and previous diagnosis of bipolar or schizoaffective disorder were included and received zotepine as monotherapy. Ten patients finished the study. Nine of them responded (50% reduction in YMRS), 5 of them within 4 days. One was an inadequate responder. Response is described by the authors as rapid. Four patients had extrapyramidal symptoms as a side effect. Unfortunately, there are no controlled studies of zotepine as yet.

Asenapine

Asenapine is not yet available for clinical use, but it has been tried in two placebo-controlled trials with overall positive results. A further advantage is that it does not seem to cause as much weight gain as other antipsychotics, such as olanzapine.

Paliperidone

Placebo-controlled trials with paliperidone are currently underway. As the active metabolite of risperidone, there is no reason to expect anything but antimanic efficacy, and a similar side-effect profile, but until the trials are finalized, little else can be said.

Summary

A summary of the current evidence available for the treatment of mania can be found in Table II (monotherapy) and Table III (combination). Obviously, there are still many gaps between the evidence from clinical trials and the use of drugs in clinical practice.
Pharmacological aspects

Electroconvulsive therapy remains an effective option for treatment-resistant mania and mixed states. Much less evidence, and in particular much less experience, is available for other techniques, such as transcranial magnetic stimulation. Psychotherapy is hard to provide during manic episodes, and there is no evidence that it may actually help; rather the opposite, Scott et al have shown that psychosocial interventions are more likely to work in patients who are in remission or minimally symptomatic. Of course, some common-sense-based, elementary educational information can and should be provided during mania, and there might be some room for more sophisticated interventions in hypomania, but the key message is that mania should be treated with pharmacotherapy, whereas relapse prevention can be an achievable goal with the combination of drug therapy and psychotherapy.

Pharmacological long-term treatment of mania

The long-term treatment of mania is indeed the long-term treatment of bipolar disorder, because not only mania, but depression, are relevant outcomes. There is far much more evidence for the long-term treatment of patients with mania as index episode than for depression, though. Maintenance medication is generally recommended following a single acute manic episode, in view of the 95% lifetime risk of recurrence. Maintenance treatment is also appropriate in patients who experience a breakthrough episode during the first year of treatment.

Nonpharmacological treatment of acute mania

Table II. Evidence base for the efficacy of drugs used to treat mania. Strength of evidence base (regardless of antimanic potency): +++, strong evidence (positive large placebo-controlled trials); ++, some evidence (from secondary outcomes of placebo-controlled trials or other randomized clinical trials); +, limited evidence (some evidence from small controlled studies or indirect evidence from clinical trials); ?, no evidence available other than open studies; -, evidence of lack of efficacy from controlled trials.

| Drug               | Acute mania | Mixed mania | Prevention of mania after mania | Prevention of depression after mania |
|--------------------|-------------|-------------|---------------------------------|--------------------------------------|
| Lithium            | +++         | +           | +                               | ++                                   |
| Valproate          | +++         | ++          | +                               | ++                                   |
| Carbamazepine      | +++         | ++          | +                               | +                                    |
| Lamotrigine        | -           | -           | +                               | +++                                  |
| Gabapentin         | -           | -           | ?                               | ?                                    |
| Topiramate         | -           | ?           | ?                               | ?                                    |
| Oxcarbazepine      | +           | +           | +                               | ?                                    |
| Lercarbazepine     | -           | -           | ?                               | ?                                    |
| Chlorpromazine     | +++         | +           | ?                               | ?                                    |
| Haloperidol        | +++         | ++          | ?                               | ?                                    |
| Clozapine          | +           | +           | ?                               | ?                                    |
| Risperidone        | +++         | +           | +                               | ?                                    |
| Olanzapine         | +++         | ++          | +++                             | +                                    |
| Quetiapine         | +++         | +           | +++                             | +                                    |
| Ziprasidone        | +++         | ++          | ?                               | ?                                    |
| Aripiprazole       | +++         | ++          | +++                             | ?                                    |
| Asenapine          | +++         | +           | ?                               | ?                                    |

Table III. Evidence base for combinations of antipsychotics with lithium or anticonvulsants. Evidence base: +, positive in at least one placebo-controlled trial; ?, no evidence available from clinical trials; -, negative results in clinical trials so far.

| Drugs          | Lithium | Valproate | Carbamazepine | Lamotrigine |
|----------------|---------|-----------|---------------|-------------|
| Chlorpromazine | ?       | ?         | ?             | ?           |
| Haloperidol    | +       | +         | ?             | ?           |
| Clozapine      | ?       | ?         | ?             | ?           |
| Risperidone    | +       | +         | -             | ?           |
| Olanzapine     | +       | +         | -             | ?           |
| Quetiapine     | +       | +         | ?             | ?           |
| Ziprasidone    | -       | -         | ?             | ?           |
| Aripiprazole   | +       | +         | ?             | ?           |
| Asenapine      | ?       | ?         | ?             | ?           |
ment following an acute episode, and in chronically ill patients with a long cycle length who do not achieve sufficient remission of acute symptoms to be classified as “recovered.”

**Lithium**

The prophylactic efficacy of lithium in bipolar I disorder has been reported for several decades, and was recently confirmed in a Cochrane review and two meta-analyses. At optimal dosing, lithium reduces recurrences by around 50%, and appears to be more effective against manic than depressive relapses. Moreover, lithium may have antisuicidal effects, independently of its efficacy in preventing recurrences. However, the efficacy of lithium in clinical practice may be less than that in controlled clinical trials, in part due to comorbidity and poor adherence. Therefore, putative predictors of a favorable response to lithium (eg, family history of bipolar disorder, no rapid cycling, complete interepisode recovery, no substance abuse, good adherence) should be also be considered. Indeed, the increased risk of relapse after sudden discontinuation of lithium, and potential for a lack of response when lithium is reintroduced, have led some experts to advise against using lithium in patients judged unwilling or unlikely to adhere to treatment for at least 2 years.

**Anticonvulsants**

**Valproate**

Despite high expectations for the prophylactic efficacy of valproate, the agent failed to demonstrate superiority over placebo in preventing recurrence of bipolar episodes in a randomized controlled trial. However, secondary analyses indicated that valproate was superior to placebo in severely ill patients and was effective in preventing new depressive episodes. In randomized studies with active comparators, valproate was equivalent to lithium and olanzapine in the prevention of bipolar recurrence. Valproate has controversially been reported to induce polycystic ovary syndrome.

**Carbamazepine**

Carbamazepine is a widely used in patients who have not responded to treatment with lithium, especially in Europe and Japan. It has been shown to be superior to placebo in a small trial, and was equal to lithium in meta-analysis. However, the studies were too heterogeneous to allow conclusive results. In a 2.5-year randomized study of lithium and carbamazepine, lithium was associated with a lower overall rate of relapse (28% vs 47%) and fewer adverse events. However, carbamazepine appeared more effective than lithium in patients with atypical features such as mixed states and delusions, suggesting it has a broader spectrum of activity. A study of treatment-naïve bipolar patients showed that lithium was slightly more effective than carbamazepine in preventing relapses over a 2-year period, although carbamazepine was superior during the first 6 months.

**Other anticonvulsants**

The evidence supporting lamotrigine prophylaxis is strong, particularly where preventing depressive episodes is a major objective, but clearly not as much as far as mania is concerned. Lamotrigine as maintenance therapy has been studied in two large randomized, controlled studies in bipolar patients with a recent depressive or manic/hypomanic episode. These studies showed that lamotrigine was superior to placebo in preventing depressive episodes and in delaying the onset of any mood episode. Furthermore, in a pooled analysis, lamotrigine was significantly better than placebo in preventing manic, hypomanic, or mixed episodes. Limited controlled data are available on the long-term outcome of bipolar patients treated with oxcarbazepine. A small study suggested that phenytoin might have some mood-stabilizing properties, and another pilot, randomized, placebo-controlled trial, suggested that gabapentin might have some prophylactic effects when used in conjunction with lithium in euthymic patients with a highly recurring course.

**Antipsychotics**

Long-term treatment with low doses of antipsychotics is not a rare practice in clinical settings when treating bipolar patients. As the first-generation antipsychotics are not effective in preventing depressive phases and could be involved in depressive relapses, they do not seem an interesting option for maintenance. However, there is growing evidence of second-generation antipsychotics having mood-stabilizing properties.
Hummel et al published a series of 3 cases (2 with bipolar disorder, 1 with schizoaffective disorder) in which mood stabilizer had been enhanced with clozapine. All of them were revisited monthly for at least 6 months before and after the addition of clozapine. Response was evaluated using the Inventory of Depressive Symptomatology (IDS), YMRS, Global Assessment of Functioning (GAF), CGI-BP, and the NIMH Life Chart Methodology, which showed improvement in all cases after clozapine was added. Weight gain and fatigue were the most common reported side effects.108

A randomized study included 38 treatment-resistant patients with schizoaffective disorder, bipolar type, and bipolar I disorder. Two groups were randomly set: 19 would receive clozapine as add-on treatment whilst 19 would be treated as usual (no clozapine was received). Both groups were followed up for 1 year. Different scales noted a significantly greater improvement in the clozapine group than in the patients not receiving clozapine.109 Atypical antipsychotics might reduce rates of emergency room visits as a group, but the effect is probably greater in the case of clozapine.110 As mentioned earlier, the problems with long-term clozapine are more weight gain and metabolic issues, rather than agranulocytosis.

Risperidone

No controlled trials are available with risperidone beyond 12 weeks, but in 2001 a large open study in 541 bipolar and schizoaffective bipolar patients was reported on. Its goal was to study whether risperidone was an effective and safe adjunction to mood stabilizers. Patients were followed for 6 months in this multicenter study. At their entry they were experiencing manic, hypomanic, mixed, or depressive episodes. After addition of risperidone, significant improvements on YMRS, HAM-D, CGI, and PANSS were noted (P<0.0001). The mean dose of risperidone was 3.9 mg/day. No new-emergent tardive dyskinesia cases were identified, and mania exacerbation within the first 6 weeks was as low as 1.8%. Although extrapyramidal symptoms and weight gain were the most common side effects reported, and were not very frequent, the authors concluded that risperidone was effective and safe when combined with mood stabilizers in the treatment of bipolar disorder and schizoaffective bipolar disorder.61 Similar conclusions were obtained in another observational study by Yatham et al.111 The same authors compared risperidone added to either lithium or valproate, finding that efficacy and safety were not related to the adjunctive mood stabilizer.112 The main issues with long-term risperidone therapy are those related with hyperprolactinamia. Trials with injectable long-acting risperidone are currently underway, but a recent open, mirror-design study suggests that it may be helpful to prevent hospitalizations due to mania and to improve treatment adherence.113

Olanzapine

Olanzapine has been widely studied and is approved by the FDA and the European Medicaments Agency (EMEA) for maintenance treatment. Several trials support its use in the maintenance phase of bipolar disorder, not only as adjunctive therapy with mood stabilizers, but also as monotherapy after successful treatment of mania. A 12-month placebo-controlled olanzapine monotherapy trial demonstrated that olanzapine was significantly superior to placebo in preventing any mood episode, including manic, depressive, and mixed recurrences.68 In a 47-week double-blind trial, 251 bipolar patients, through a manic or mixed episode, were randomized to olanzapine (n=125) or divalproex (n=126) Efficacy was rated with the YMRS (at least 20 for inclusion, lower than 12 for remission, and higher than 15 for relapse) At end point the olanzapine group achieved significantly greater mean improvement in YMRS. Nevertheless, no difference was noted in rates of bipolar relapse between both treatments. Some olanzapine-treated patients presented somnolence, dry mouth, increased appetite, weight gain, akathisia, and high alanine aminotransferase levels, while nausea and nervousness were reported by the divalproex-treated patients.96 Olanzapine was compared with lithium in a double-blind trial comprising 431 patients. After 52 weeks, olanzapine was similar to lithium in preventing depressive episodes, but superior in preventing manic or mixed relapses.114 This study suggested olanzapine’s efficacy in relapse prevention, which was tested in a double-blind placebo-controlled 12-month clinical trial. Patients with an acute manic or mixed episode received olanzapine for 6-12 weeks. Those who remitted were randomized to olanzapine (n=225) or placebo (n=136) and joined a double-blind 52-week trial. Olanzapine was superior to placebo in preventing any kind of bipolar relapse (46.7% vs 80.1%; P<0.001) and
relapse into a manic episode (16.4% vs 41.2%; P<0.001) or a depressive episode (34.7% vs 47.8%, P=0.015). Side effects were more prominent in the olanzapine-treated group (weight gain, fatigue, and akathisia) than in the placebo group. More patients finished the study in the olanzapine group.\textsuperscript{114}

Efficacy of olanzapine combined with a mood stabilizer in prevention of bipolar relapses was studied in an 18-month double-blind study. At the starting point, patients scored at least 16 on the YMRS. Fifty-one were randomized to olanzapine and 48 to placebo. Both groups received lithium or valproate semisodium. Median time to bipolar symptomatic relapse was significantly higher in the olanzapine-mood stabilizer group (163 vs 42 days; P=0.023), but there were no differences in time to bipolar syndromic relapse (94 vs 40.5 days; P=0.742).\textsuperscript{115}

Olanzapine is one of the best-studied second-generation antipsychotics in bipolar disorder. The main downside for its use in maintenance is its propensity to induce weight gain and the risk of metabolic syndrome.\textsuperscript{63}

Quetiapine

After some preliminary evidence from open, non-controlled trials,\textsuperscript{116} controlled trials of quetiapine in maintenance have just been finalized, showing for the first time a positive outcome with regard to prevention of manic and depressive recurrences from either manic, mixed, or depressive index episode in a 2-year placebo-controlled add-on study.\textsuperscript{117} Importantly, patients were enrolled while manic, depressed, or mixed, and were required to be stable for at least 12 weeks before randomization. The main shortcomings of quetiapine in this indication are persistent sedation and weight gain, which is significantly lower than with clozapine or olanzapine, but still relevant, and also some signal of glucose increase. These issues can sometimes be partially addressed by adjusting the dose downwards.

Ziprasidone

There are no controlled long-term trials with ziprasidone in bipolar disorder to date. The open extension phase of some of the acute trials suggests that it could be helpful as augmentation therapy in a relatively well-tolerated way, but this should be confirmed in future controlled trials,\textsuperscript{118} which might confirm its potential effectiveness and low propensity to cause weight gain, in contrast with the majority of antipsychotics.

Aripiprazole

Aripiprazole is approved by the FDA for maintenance treatment. To date there is only one relapse prevention study with aripiprazole. A 26-week double-blind trial admitted euthymic patients (YMRS not higher than 10 and Montgomery-Asberg Depression Rating Scale (MADRS) not higher than 13 during four visits or 6 weeks) and randomized them to aripiprazole (n=78) or placebo (n=83). The aripiprazole group had a significantly lower percentage of manic relapses, but there were no statistical differences in depressive relapses between groups.\textsuperscript{119}

Amisulpride

Only one, methodologically limited study is available so far in bipolar maintenance with this compound. Carta and coworkers\textsuperscript{120} reported positive outcomes using amisulpride as adjunctive long-term pharmacotherapy in 14 bipolar I patients.

Nonpharmacological long-term treatment

Electroconvulsive therapy

The use of maintenance electroconvulsive therapy is more supported by anecdotal experience than by scientific evidence, but has been reported as a useful and safe strategy for treatment-resistant patients.\textsuperscript{121,122}

Psychoeducation

Interventions based on intensive education for patients or relatives have proved to be useful for the prevention of further episodes,\textsuperscript{123-126} but mostly if applied when the patient is not acutely ill.\textsuperscript{14} The evidence for pure cognitive-behavioral interventions is controversial,\textsuperscript{127-129} as well as for interpersonal and social rhythm therapy,\textsuperscript{130,131} and practically absent for other types of interventions, such as psychoanalytical therapy. The active ingredients of the effective therapies seem to be those related to enhanced medication adherence, illness awareness and skills for the detection of prodromal signs of relapse, avoidance of drug misuse, stabilization of sleep and other rhythms, and coping strategies when faced with stress.\textsuperscript{132}
Pharmacological aspects

Conclusions

In summary, the treatment of mania still poses very important challenges, particularly as far as the long term is concerned. In the last decade, a number of new drugs have proved to be effective and have increased our treatment armamentarium for this condition, resulting in more compounds receiving an indication in the treatment of acute mania and maintenance treatment. Currently, lithium, valproate, carbamazepine, chlorpromazine, haloperidol, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are indicated for the treatment of acute mania in the majority of European countries and North America, with some minor variations from country to country, and lithium, valproate, lamotrigine, olanzapine, aripiprazole, and quetiapine are indicated for maintenance treatment, again depending on the country. However, the gap between evidence base and clinical practice is still huge, and the majority of patients have to be treated with combinations of several drugs and psychosocial interventions in order to achieve a reasonable outcome from the clinical as well as functional point of view. This may be particularly true for patients with rapid-cycling bipolar disorder, who may need complex combinations of therapies and sometimes physical treatments such as electroconvulsive therapy to achieve clinical stability. For these patients, as well as for those with mixed states, for those with enduring subsyndromal symptoms, and ultimately for the majority of people with bipolar disorder, more efficacious, tolerable treatments are badly needed.

Supported in part by grants from the Stanley Medical Research Institute and Instituto Carlos III (Fondos de Investigación Sanitaria y CIBER-SAM). Dr Vieta has acted as consultant, received grants, or been hired as speaker by the following companies: Almirall, Astra-Zeneca, Bial, Bristol-Myers-Squibb, Eli-Lilly, Esteve, Glaxo-Smith-Kline, Janssen-Cilag, Lundbeck, Merck-Sharpe-Dohme, Novartis, Organon, Pfizer, Sanofi, Servier, and UCB.

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Tratamiento a corto y largo plazo de la manía

El tratamiento de la manía comienza con un diagnóstico correcto y medidas elementales para prevenir riesgos para el paciente, familiares, y terceras personas. En ocasiones, el ingreso y tratamiento involuntarios son necesarios durante algunos días. Los pacientes con manía psicótica o mixta pueden ser más difíciles de tratar. Actualmente existen pruebas sólidas de la eficacia del litio, los antiepilépticos valproato y carbamazepina, y los antipsicóticos clorpromacina, haloperidol, risperidona, olanzapina, quetiapina, ziprasidona, aripiprazol, y asenapina en la manía aguda, y también indicios de la eficacia de la clozapina y de la terapia electroconvulsiva en casos resistentes al tratamiento. Sin embargo, en la práctica clínica, el tratamiento combinado es la norma más que la excepción. El tratamiento de la manía requiere una visión a largo plazo, y los fundamentos científicos podrían ser más sólidos para unos compuestos que otros. A la hora de tomar decisiones respecto al tratamiento, la tolerabilidad debería ser una cuestión fundamental, ya que las diferencias en seguridad y tolerabilidad pueden ser mayores que las de eficacia entre fármacos. La psicoeducación de pacientes y familiares es una herramienta poderosa que debería combinarse con el tratamiento farmacológico para un mejor pronóstico a largo plazo. La recuperación funcional debería ser la meta final.

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Tratamiento a corto y largo plazo de la manía

Le traitement de l'état maniaque débute par un diagnostic adéquat et des mesures élémentaires pour éviter de mettre en péril le patient, ses proches et autrui. Il faut parfois imposer une hospitalisation et un traitement pendant quelques jours, car les patients psychotiques ou maniaques mixtes peuvent être plus difficiles à traiter. À l’heure actuelle, des arguments sérieux sont en faveur de l’utilisation du lithium, des anticonvulsivants comme le valproate et la carbamazépine, et des antipsychotiques comme la chlorpromazine, l’halopéridol, la rispéridone, l’olanzapine, la quetiapine, la ziprasidone, l’aripiprazole et l’asénapine au cours de l’état maniaque aigu. D’autres observations mettent en avant l’utilisation de la clozapine ou des électrochocs dans les cas réfractaires au traitement. Cependant, en pratique clinique, l’association de plusieurs traitements est la règle plutôt que l’exception. Le traitement de l’état maniaque mérite une vision à long terme, et les fondements de certains traitements peuvent être plus forts que d’autres. Lorsque la décision du traitement est prise, il faut aussi prendre en compte la tolérance, car des différences d’innocuité et de tolérance peuvent supplanter des différences d’efficacité pour la plupart des produits. L’éducation psychologique des patients et des soignants est un outil puissant qui devrait être utilisé en association avec le traitement pour des résultats optimaux à long terme. La guérison fonctionnelle du patient devrait être l’objectif final.
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