Acute and long-term treatment of mania

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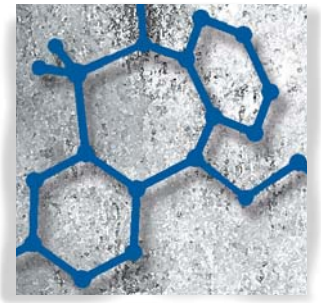

The treatment of mania starts with a correct diagnosis and elementary measures to prevent risks for the patient, relatives, and others. Sometimes, compulsory admission and treatment may be required for a few days. Patients with psychotic or mixed mania may be more difficult to treat. At the present time, 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.

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Manic-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.[1] It is characterized by the recurrence of mania, depression, or mixed episodes.[2] Mania is the most characteristic phase of bipolar disorder, and a major cause of disability, stigma, and cognitive impairment.[3,4] 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.[5] 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.[6,7] 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

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states and rapid cycling. 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. For this reason, 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.[15] 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.[16] 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.[17]

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.[18] 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.[19,20]

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[21] In a three-arm randomized study comparing placebo, lithium, and valproate, lithium and valproate were similarly effective in improving manic symptoms.[22]

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.[23] By contrast, two double-blind studies[24,25] 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.[26]

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.[22,27] 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.[17] Valproate may not be as efficacious as antipsychotics such as olanzapine[28,29]), but is generally better tolerated.[30] An extended-release form of valproate is also available and proven to be effective in mania.[31] 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.[32] Other potential acute side effects of valproate are weight gain and hair loss.

Carbamazepine

Since its introduction into psychiatric treatment,[33] 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.[34] 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.[35,36] 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,[37] while the other found the drugs to be equivalent.[38] 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.[39]

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, levetirazetam, pregabalin, or zonisamide. There is some limited evidence that phenytoin may possess antimanic effects.[40] Oxcarbazepine, structurally similar to carbamazepine, may possess antimanic effects,[41] but licarbazepine, its main active metabolite, failed in at least one placebo-controlled trial. Clearly, not all anticonvulsants are antimanics.

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[42] and a few comparative, randomized studies, versus lithium, haloperidol, and pimozide.[43-45] 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,[46,47] 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.[48] Haloperidol has been compared as monotherapy with placebo, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and as an add-on to placebo and risperidone.[46-52]

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.[53] 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.[54]

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[58] At 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.[48] 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[59] but further trials[60-62] 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[64] or 4[65] 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

divalproex group.[28] 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.[30]
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.[67] 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.[68] 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; $P<0.001$).[47]
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.[21]
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.[69]
Two randomized, double-blind, placebo-controlled studies were designed to evaluate the efficacy and tolerability of quetiapine when adjuncted 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%; $P=0.007$).[70] In the second study, quetiapine did not separate from placebo at study end point.[71] 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[72] 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.[73] 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.[52,74]
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.[75] 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 D_2/D_3 and serotonin $(5\text{-HT})_{1A}$ receptors and an antagonist of

5-HT_{2A} and histamine H_1 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.[76]

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.[77,78]

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,[51] 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.[79] 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.[80] 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.[80] Amisulpride may carry some risk of extrapyramidal side effects and hyperprolactinemia.

Zotepine

A group from Germany has recently reported an open study with zotepine.[81] Zotepine blocks D_1, D_2, 5-HT_1, and 5-HT_2 receptors. It behaves as a noradrenaline reuptake inhibitor and antagonizes muscarine acetylcholine (mAch) and H_1 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.[82] A further advantage is that it does not seem to cause as much weight gain as other antipsychotics, such as olanzapine.[83]

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.

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

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.

Nonpharmacological treatment of acute mania

Electroconvulsive therapy remains an effective option for treatment-resistant mania and mixed states.[9,10] 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[84] 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,[85] 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 treat-

Drugs	Lithium	Valproate	Carbamazepine	Lamotrigine
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

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[86] and two meta-analyses.[87,88] At optimal dosing, lithium reduces recurrences by around 50%, and appears to be more effective against manic than depressive relapses.[89,90] Moreover, lithium may have antisuicidal effects, independently of its efficacy in preventing recurrences.[19,20,91] 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.[92] 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.[18]

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.[93] 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[94,95] and olanzapine[96] 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,[97] and was equal to lithium in meta-analysis.[98] 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.[99] However, carbamazepine appeared more effective than lithium in patients with atypical features such as mixed states and delusions,[100] 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.[101]

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[89] or manic/hypomanic episode.[90] 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.[102] Limited controlled data are available on the long-term outcome of bipolar patients treated with oxcarbazepine.[41,103] A small study suggested that phenytoin might have some mood-stabilizing properties,[104] 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.[105]

Antipsychotics

Long-term treatment with low doses of antipsychotics is not a rare practice in clinical settings when treating bipolar patients.[106] As the first-generation antipsychotics are not effective in preventing depressive phases and could be involved in depressive relapses,[107] they do not seem an interesting option for maintenance. However, there is growing evidence of second-generation antipsychotics having mood-stabilizing properties.[6]

Clozapine

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.[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; $P=0.742$).[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.[63]

Quetiapine

After some preliminary evidence from open, non-controlled trials,[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.[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,[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.[119]

Amisulpride

Only one, methodologically limited study is available so far in bipolar maintenance with this compound. Carta and coworkers[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.[121,122]

Psychoeducation

Interventions based on intensive education for patients or relatives have proved to be useful for the prevention of further episodes,[123-126] but mostly if applied when the patient is not acutely ill.[84] The evidence for pure cognitive-behavioral interventions is controversial,[127-129] as well as for interpersonal and social rhythm therapy,[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, stabilitzation of sleep and other rhythms, and coping strategies when faced with stress.[132]

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. ❑

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REFERENCES

1. World Health Organization. *The World Health Report 2001;Mental Health: New Understanding. New Understanding, New Hope*. Geneva, Switzerland: World Health Organization; 2001.
2. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 2nd ed. New York, NY: Oxford University Press; 2007.
3. Martinez-Aran A, Vieta E, Colom F, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord*. 2004;6:224-232.
4. Martinez-Aran A, Vieta E, Reinares M, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry*. 2004;161:262-270.
5. Vieta E, Rosa AR. Evolving trends in the long-term treatment of bipolar disorder. *World J Biol Psychiatry*. 2007;8:4-11.
6. Vieta E, Goikolea JM. Atypical antipsychotics: newer options for mania and maintenance therapy. *Bipolar Disord*. 2005;7(suppl 4):21-33.
7. Berk M, Dodd S. Efficacy of atypical antipsychotics in bipolar disorder. *Drugs*. 2005;65:257-269.
8. Vieta E, Panicali F, Goetz I, et al. Olanzapine monotherapy and olanzapine combination therapy in the treatment of mania: 12-week results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) observational study. *J Affect Disord*. 2008;106:63-72.
9. Fink M. ECT in therapy-resistant mania: does it have a place? *Bipolar Disord*. 2006;8:307-309.
10. Valenti M, Benabarre A, Garcia-Amador M, et al. Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. *Eur Psychiatry*. 2008;23:53-56.
11. Vieta E. Bipolar mixed states and their treatment. *Expert Rev Neurother*. 2005;5:63-68.
12. Vieta E. The treatment of mixed states and the risk of switching to depression. *Eur Psychiatry*. 2005;20:96-100.
13. Colom F, Vieta E, Daban C, et al. Clinical and therapeutic implications of predominant polarity in bipolar disorder. *J Affect Disord*. 2006;93:13-17.
14. Vieta E. *Managing Bipolar Disorder in Clinical Practice*. London, UK: Current Medicine Group Ltd; 2007.
15. Fountoulakis KN, Vieta E, Sanchez-Moreno J, et al. Treatment guidelines for bipolar disorder: a critical review. *J Affect Disord*. 2005;86:1-10.
16. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. *J Clin Psychiatry*. 1998;59(suppl 6):13-19.
17. Swann AC, Bowden CL, Morris D, et al. Depression during mania. Treatment response to lithium or divalproex. *Arch Gen Psychiatry*. 1997;54:37-42.
18. 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;164:149-152.
19. Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord*. 2006;8:625-639.
20. Gonzalez-Pinto A, Mosquera F, Alonso M, et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord*. 2006;8:618-624.
21. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry*. 2005;66:111-121.
22. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA*. 1994;271:918-924.
23. Vieta E. Atypical antipsychotics in the treatment of mood disorders. *Curr Opin Psychiatry*. 2003;16:23-27.
24. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. *J Affect Disord*. 1980;2:279-288.
25. Johnstone EC, Crow TJ, Frith CD, et al. The Northwick Park "functional" psychosis study: diagnosis and treatment response. *Lancet*. 1988;2:119-125.
26. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. *Am J Psychiatry*. 1998;155:12-21.
27. Pope HG, Jr., McElroy SL, Keck PE, Jr, et al. Valproate in the treatment of acute mania. A placebo-controlled study. *Arch Gen Psychiatry*. 1991;48:62-68.
28. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry*. 2002;159:1011-1017.
29. Vieta E. Divalproex versus olanzapine in mania. *J Clin Psychiatry*. 2003;64:1266-1267.
30. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry*. 2002;63:1148-1155.

Tratiamento a corto y lungo plazo de la mania

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 solidas de la eficacia del litio, los antiepilépticos valproato y carbamazepina, y los antipsicoticos clorpromacina, haloperidol, risperidona, olanzapina, quetiapina, ziprasidona, aripiprazol, y asenapina en la mania 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 mas 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.

Traitement aigu et à long terme de l'état maniaque

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 quétiapine, 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.

31. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry*. 2006;67:1501-1510.
32. Curtis D, Kerr M. NICE recommendations for valproate treatment are unhelpful. *Br J Psychiatry*. 2005;186:447.
33. Okuma T. Effects of carbamazepine and lithium on affective disorders. *Neuropsychobiology*. 1993;27:138-145.
34. Ballenger JC, Post RM. Therapeutic effects of carbamazepine in affective illness: a preliminary report. *Commun Psychopharmacol*. 1978;2:159-175.
35. Weisler RH, Kalali AH, Ketter TA. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry*. 2004;65:478-484.
36. Weisler RH, Keck PE, Jr, Swann AC, et al. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2005;66:323-330.
37. Lerer B, Moore N, Meyendorff E, et al. Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry*. 1987;48:89-93.
38. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry*. 1991;48:915-921.
39. Small JG, Klapper MH, Marhenke JD, et al. Lithium combined with carbamazepine or haloperidol in the treatment of mania. *Psychopharmacol Bull*. 1995;31:265-272.
40. Mishory A, Yaroslavsky Y, Bersudsky Y, et al. Phenytoin as an antimanic anticonvulsant: a controlled study. *Am J Psychiatry*. 2000;157:463-465.
41. Popova E, Leighton C, Bernabarre A, et al. Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Exp Rev Neurother*. 2007;7:617-626.
42. Klein DF. Importance of psychiatric diagnosis in prediction of clinical drug effects. *Arch Gen Psychiatry*. 1967;16:118-126.
43. Prien RF, Caffey EM, Jr., Klett CJ. Comparison of lithium carbonate and chlorpromazine in the treatment of mania. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. *Arch Gen Psychiatry*. 1972;26:146-153.
44. Shopsin B, Gershon S, Thompson H, et al. Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine, and haloperidol. *Arch Gen Psychiatry*. 1975;32:34-42.

45. Cookson J, Silverstone T, Wells B. Double-blind comparative clinical trial of pimozide and chlorpromazine in mania. A test of the dopamine hypothesis. *Acta Psychiatr Scand*. 1981;64:381-397.

46. Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol*. 2005;15:75-84.

47. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania - a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2005;15:573-585.

48. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Arch Gen Psychiatry*. 2003;60:1218-1226.

49. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry*. 2002;159:1146-1154.

50. Muller-Oerlinghausen B, Retzow A, Henn FA, et al. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. European Valproate Mania Study Group. *J Clin Psychopharmacol*. 2000;20:195-203.

51. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005;187:235-242.

52. Vieta E, Ramey T, Keller D, et al. Ziprasidone in the treatment of acute mania: A 12-week placebo-controlled, haloperidol referenced study. *J Psychopharmacol*. In press.

53. McElroy SL, Dessain EC, Pope HG, Jr, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry*. 1991;52:411-414.

54. Barbini B, Scherillo P, Benedetti F, et al. Response to clozapine in acute mania is more rapid than that of chlorpromazine. *Int Clin Psychopharmacol*. 1997;12:109-112.

55. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. *Am J Psychiatry*. 1996;153:759-764.

56. Hirschfeld RM, Keck PE, Jr., Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2004;161:1057-1065.

57. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania: Double-blind, placebo-controlled study. *Br J Psychiatry*. 2005;187:229-234.

58. Yatham LN, Grossman F, Augustyns I, et al. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *Br J Psychiatry*. 2003;182:141-147.

59. Dwight MM, Keck PE, Jr., Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. *Lancet*. 1994;344:554-555.

60. Vieta E, Herraiz M, Parramon G, et al. Risperidone in the treatment of mania: efficacy and safety results from a large, multicentre, open study in Spain. *J Affect Disord*. 2002;72:15-19.

61. Vieta E, Goikolea JM, Corbella B, et al. Risperidone safety and efficacy in the treatment of bipolar and schizoaffective disorders: results from a 6-month, multicenter, open study. *J Clin Psychiatry*. 2001;62:818-825.

62. Vieta E, Herraiz M, Fernandez A, et al. Efficacy and safety of risperidone in the treatment of schizoaffective disorder: initial results from a large, multicenter surveillance study. Group for the Study of Risperidone in Affective Disorders (GSRAD). *J Clin Psychiatry*. 2001;62:623-630.

63. Vieta E. Olanzapine in bipolar disorder. *Exp Opin Pharmacother*. 2004;5:1613-1619.

64. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *Am J Psychiatry*. 1999;156:702-709.

65. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Arch Gen Psychiatry*. 2000;57:841-849.

66. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol*. 1999;14:339-343.

67. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry.* 2002;59:62-69.

68. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry*. 2006;163:247-256.

69. Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Curr Med Res Opin*. 2005;21:923-934.

70. Sachs G, Chengappa KN, Suppes T, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2004;6:213-223.

71. Yatham LN, Vieta E, Young AH, et al. A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. *Int Clin Psychopharmacol*. 2007;22:212-220.

72. Keck PE, Jr., Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003;160:741-748.

73. Potkin SG, Keck PE, Jr., Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005;25:301-310.

74. Fountoulakis KN, Vieta E, Siamouli M, et al. Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder. *Ann Gen Psychiatry.* 2007;6:27.

75. Weisler R, Dunn J, English P. Ziprasidone in adjunctive treatment of acute bipolar mania: randomized, double-blind, placebo-controlled trial. Paper presented at:16th European College of Neuropsychopharmachology Congress. Prague, Czech Republic; 20-24 September. 2003.

76. Lyseng-Williamson KA, Perry CM. Aripiprazole: in acute mania associated with bipolar I disorder. *CNS Drugs*. 2004;18:367-376.

77. Keck PE, Jr., Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003;160:1651-1658.

78. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006;20:536-546.

79. Vieta E, T'joen C, McQuade RD, et al. Efficacy of adjunctive aripiprazole to valproate or lithium in bipolar patients with mania who were partially non-reponsive to valproate/lithium: A placebo-controlled study. *Am J Psychiatry*. 2008. In press.

80. Vieta E, Ros S, Goikolea JM, et al. An open-label study of amisulpride in the treatment of mania. *J Clin Psychiatry*. 2005;66:575-578.

81. Amann B, Sterr A, Mergl R, et al. Zotepine loading in acute and severely manic patients: a pilot study. *Bipolar Disord*. 2005;7:471-476.

82. McIntyre R, Panagides J, Alphs L, et al. Treatment of mania in bipolar I disorder: a placebo- and olanzapine-controlled trial of asenapine (ARES 7501005). Paper presented at: 20th ECNP Congress. Vienna, Austria; October 13-17, 2007.

83. McIntyre R, Panagides J, Alphs L, et al. Efficacy and tolerability of asenapine and olanzapine in acute mania: A double-blind extension study (ARES 7501006). Paper presented at: 20th ECNP Congress. Vienna, Austria; October 13-17, 2007.

84. Scott J, Colom F, Vieta E. A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. *Int J Neuropsychopharmacol*. 2007;10:123-129.

85. Colom F, Vieta E. Sudden glory revisited: cognitive contents of hypomania. *Psychother Psychosom*. 2007;76:278-288.

86. Burgess S, Geddes J, Hawton K, et al. Lithium for maintenance treatment of mood disorders. *Cochrane Database Syst Rev*. 2001;CD003013.

87. Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatr Scand*. 1999;100:406-417.

88. Geddes JR, Burgess S, Hawton K, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry*. 2004;161:217-222.

89. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64:1013-1024.
90. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60:392-400.
91. Goodwin FK, Fireman B, Simon GE, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA*. 2003;290:1467-1473.
92. Abou-Saleh MT, Coppen A. Who responds to prophylactic lithium? *J Affect Disord*. 1986;10:115-125.
93. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry*. 2000;57:481-489.
94. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry*. 2005;162:2152-2161.
95. Lambert P, Venaud G. Comparative study of valpromide versus lithium in treatment of affective disorders. *Nervure*. 1992;5:57-65.
96. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry*. 2003;160:1263-1271.
97. Okuma T, Inanaga K, Otsuki S, et al. A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. *Psychopharmacology*. (Berl) 1981;73:95-96.
98. Dardennes R, Even C, Bange F, et al. Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders. A meta-analysis. *Br J Psychiatry*. 1995;166:378-381.
99. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders--a randomised study. *J Affect Disord*. 1997;43:151-161.
100. Greil W, Kleindienst N, Erazo N, et al. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J Clin Psychopharmacol*. 1998;18:455-460.
101. Hartong EG, Moleman P, Hoogduin CA, et al. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. *J Clin Psychiatry*. 2003;64:144-151.
102. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry*. 2004;65:432-441.
103. Vieta E. Maintenance therapy for bipolar disorder: current and future management options. *Exp Rev Neurother*. 2004;4:S35-S42.
104. Mishory A, Winokur M, Bersudsky Y. Prophylactic effect of phenytoin in bipolar disorder: a controlled study. *Bipolar Disord*. 2003;5:464-467.
105. Vieta E, Manuel GJ, Martinez-Aran A, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry*. 2006;67:473-477.
106. Sernyak MJ, Woods SW. Chronic neuroleptic use in manic-depressive illness. *Psychopharmacol Bull*. 1993;29:375-381.
107. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr Neuropsychopharmakol*. 1980;13:156-167.
108. Hummel B, Dittmann S, Forsthoff A, et al. Clozapine as add-on medication in the maintenance treatment of bipolar and schizoaffective disorders. A case series. *Neuropsychobiology*. 2002;45(suppl 1):37-42.
109. Suppes T, Webb A, Paul B, et al. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am J Psychiatry*. 1999;156:1164-1169.
110. Brown ES, Thomas NR, Carmody T, et al. Atypical antipsychotics in bipolar and schizoaffective disorders. *Pharmacopsychiatry*. 2001;34:80-81.
111. Yatham LN, Binder C, Riccardelli R, et al. Risperidone in acute and continuation treatment of mania. *Int Clin Psychopharmacol*. 2003;18:227-235.
112. Yatham LN, Binder C, Kusumakar V, et al. Risperidone plus lithium versus risperidone plus valproate in acute and continuation treatment of mania. *Int Clin Psychopharmacol*. 2004;19:103-109.
113. Vieta E, Nieto E, Autet A, et al. A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. *World J Biol Psychiatry*. 2008. In press.
114. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*. 2005;162:1281-1290.
115. Tohen M, Chengappa KN, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry*. 2004;184:337-345.
116. Sajatovic M, Brescan DW, Perez DE, et al. Quetiapine alone and added to a mood stabilizer for serious mood disorders. *J Clin Psychiatry*. 2001;62:728-732.
117. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. In press.
118. Weisler R, Warrington L, Dunn J, et al. Adjunctive ziprasidone in bipolar mania: short and long-term data. Program and abstracts of the American Psychiatric Association, Annual Meeting. New York, NY; May 1-6, 2004.
119. Keck PE, Jr, Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry*. 2006;67:626-637.
120. Carta MG, Zairo F, Mellino G, et al. An open label follow-up study on amisulpride in the add-on treatment of bipolar I patients. *Clin Pract Epidemol Ment Health*. 2006;2:19.
121. Sienaert P, Peuskens J. Electroconvulsive therapy: an effective therapy of medication-resistant bipolar disorder. Bipolar Disord. 2006;8:304-306.
122. Tsao CI, Jain S, Gibson RH, et al. Maintenance ECT for recurrent medication-refractory mania. *J ECT*. 2004;20:118-119.
123. Perry A, Tarrier N, Morriss R, et al. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *BMJ*. 1999;318:149-153.
124. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry*. 2003;60:402-407.
125. Miklowitz DJ, Wisniewski SR, Miyahara S, et al. Perceived criticism from family members as a predictor of the one-year course of bipolar disorder. *Psychiatry Res*. 2006;144:153-166.
126. Reinares M, Colom F, Sanchez-Moreno J, et al. Impact of caregivers group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial. *Bipolar Disord*. 2008;10:511-519.
127. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry*. 2006;188:313-320.
128. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Arch Gen Psychiatry*. 2003;60:145-152.
129. Lam D, Wright K, Smith N. Dysfunctional assumptions in bipolar disorder. *J Affect Disord*. 2004;79:193-199.
130. Frank E. Interpersonal and social rhythm therapy: a means of improving depression and preventing relapse in bipolar disorder. *J Clin Psychol*. 2007;63:463-473.
131. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biol Psychiatry*. 2000;48:593-604.
132. Colom F, Vieta E. *Psychoeducation Manual for Bipolar Disorder*. Cambridge, UK: Cambridge University Press; 2006.