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Systematic Review

Drug therapy for bipolar disorder: A review of efficacy evidence

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Abstract

The purpose of this article is to provide scientific evidence on mood stabilizers used in the treatment of bipolar disorder. Indeed, it has proven difficult to develop drugs for this disorder, particularly in long-term treatment for relapse prevention. We review the main drugs that have obtained approval for use in the European Union and the United States. We take again the clinical studies which provided the basis for the evaluations. These studies are few in number and relatively old as it is difficult to conduct them in bipolar disorder. These are studies in monotherapy but also in dual therapy which better reflects the daily use of these drugs.

Introduction

Over the past few decades, a growing number of therapeutic strategies (medicated or not) have been developed and validated in the treatment of bipolar disorders. The multiplication of these therapeutic advances constitutes a new challenge for practitioners in the therapeutic choice for bipolar patients. As part of an evidence-based medicine approach, professional guidelines have been developed for the treatment of bipolar disorder to help the physician decide on the appropriate care for specific clinical circumstances.

Management of bipolar disorder aims to reduce the severity and number of episodes of depression and mania to allow for as normal a life as possible. To do this, it is useful for the patient to know some basic elements of the prescribed drugs. This is to better perceive their positive effects. Indeed, at the beginning of the treatment, the patient often has the impression of its ineffectiveness, it is often the relatives who note an improvement. Patients pay more attention to the potential side effects of drugs than to their benefits. This is especially true when it comes to mood regulation. The episodic and chronic nature of bipolar disorder usually requires long-term treatment in all patients, yet there is an unmet need for well-tolerated and clinically effective maintenance therapy with enhanced patient adherence.

Bipolar disorder treatment options

If a person is left untreated, episodes of bipolar mania can last between 3 and 6 months. Episodes of depression tend to last longer, often 6 to 12 months.

Most patients with bipolar disorder can be treated by combining different treatments. These may include one or more of the following:

- *Medicines to prevent episodes of mania and depression -these are called mood stabilizers -and patients take them daily on a long-term basis*

- *Medicines to treat the main symptoms of depression or mania when they occur*

- *Psychological treatment - such as talking therapies, which*

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help manage depression and give advice on how to improve relationships

- *Lifestyle tips - like exercising regularly, planning activities that one enjoys and that give one a sense of accomplishment and tips for improving the diet and sleeping better.*

Hospital treatment may be needed if symptoms are severe or if the patient is being treated under mental health law because there is a risk of harming themselves or others. Under certain circumstances, he could receive treatment in a day hospital and therefore return home in the evening.

Mood stabilizers

Lithium: It is the first mood stabilizer that was used on an empirical basis before its effectiveness in the prevention of depressive or manic episodes was validated by placebo-controlled studies [1]. Its mechanism of action is not yet clearly and fully elucidated. The mechanisms of action of lithium-ion in mood disorders are currently uncertain. Lithium reduces dopaminergic (inhibition of its release caused by calcium-dependent depolarization) and glutamatergic (action on the expression of the NMDA receptor, increase in glutamate reuptake) activity. The mechanisms of action of this ion would involve an effect at the level of the second messengers (inhibition of protein kinase C, inositol monophosphate, etc.) which underlie its modulating action on neurotransmission. Conversely, lithium seems to increase GABAergic activity and the release of serotonin (action on the 5HT1B receptor). Lithium seems to have several pathways of action that are undoubtedly interconnected and can influence in particular second messengers as well as the regulation of the expression of genes involved in the production of growth factors and neuronal plasticity [2]. Lithium's therapeutic mechanism involves the maintenance of Endoplasmic Reticulum (ER) homeostasis via increased Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) gene expression mediated by the Activator Protein-1 (AP-1) transcription factor [3]. Furthermore, lithium would reduce cellular oxidative stress (regulation of mitochondrial complexes 1 and 2) but would facilitate the action of a neurotrophic factor, the "Brain Derived Neurotrophic Factor" and would increase the level of BCL-2 (protein regulating the pathways leading to cell apoptosis) [4].

Lithium is the main drug used to treat bipolar disorder in some countries, given its lower cost; it is also a historic product for preventing manic and depressive attacks [5]. However, when a patient is taking lithium, they should avoid using Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as ibuprofen, unless prescribed by the GP, as these drugs compete with lithium for sodium elimination. It is the same with diuretics often used as antihypertensives [6].

In the use of lithium context, it is important to respect the prescribed dose and not to stop it abruptly. For lithium to be effective, the dosage must be correct [7]. Too high dosage could lead to side effects:

- Digestive: nausea, vomiting, diarrhea.

- Neurological: sedation, slowing down, fine hand tremors, dizziness.

- Muscular: hypotonia, rarely jerky movements of the arms and legs.

Oral absorption of lithium is complete and the maximum plasma concentration is two to four hours after taking a non-depot form. The mean plasma half-life of lithium is 22 hours. Its concentration in plasma recognized as effective in therapy ranges from 0.5 to 0.8 mmol/L [8]. This is the residual level; the blood sample being taken in the morning before the first daily dose or in the evening before the single dose of a prolonged-release form. Its volume of distribution is close to 0.8 l/kg, which corresponds to a very wide distribution, equal to that of total water. Although lithium is not bound to plasma proteins, its passage through the brain and cerebrospinal fluid is slow, and at equilibrium, cerebrospinal fluid contains about 40% of the plasma concentration. Elimination is more than 95% urinary and any renal insufficiency delays it [9]. About 80% of the lithium filtered by the glomerulus is reabsorbed at the level of the proximal tubule; its clearance is about 20% of that of creatinine. Decreasing sodium intake increases lithium retention by the kidney and vice versa [10].

The patient should inform the doctor immediately if he experiences any side effects while taking lithium. This requires regular blood tests, at least every 3 to 6 months. To ensure that blood lithium concentrations (lithemia) are neither too high nor too low. During changes in diet or season (summer, winter), it is possible to observe variations in lithium levels. One should try to have a blood concentration of 0.5 or 0.6 mmol / l and never exceed 1 mmol / l [8].

Renal and thyroid function should also be checked every 2 to 3 months when adjusting the lithium dose, and every 12 months in all other cases [9].

Long used to treat TBI, lithium has been used successfully to treat TB II; but currently, preference is given to anticonvulsants and antipsychotics that have fewer long-term harms [11].

Anticonvulsants: Anticonvulsant drugs (because previously used in the treatment of epilepsy) include valproate, carbamazepine, and lamotrigine.

These drugs are sometimes used to treat manic episodes. They are also long-term mood stabilizers.

An anticonvulsant drug can be used alone or in combination with lithium or with another anticonvulsant when bipolar disorder does not respond to lithium alone.

Valproic acid: The mechanism of action of valproic acid is complex, calling for a decrease in neuronal hyperexcitability both by strengthening GABAergic transmission and by inhibiting sodium and especially calcium ion channels. Valproic acid activates or inhibits the various targets by direct routes or by unknown mechanisms. Cellular targets of acid valproic histone deacetylase are HDACs, ion channels, the level of GABA, phospholipase A2 signaling pathway, synthesis of inositol and

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resulting phospholipids, the pathway of MAP Kinases and GSK3. These complex mechanisms of action may account for the many therapeutic uses of valproic acid [12].

Pharmacokinetic studies show that the blood bioavailability of valproate is close to 100%. The half-life of the molecule is 15 to 17 hours and the equilibrium plasma concentration is reached in 3 to 4 days [13]. Valproate is contraindicated in acute and chronic hepatitis, or even a family history of hepatitis because one of the major side effects is the induction of sometimes severe liver damage [14].

Valproate is generally not prescribed to women of childbearing age, but there is a risk of physical defects in newborn babies, such as spina bifida (lack of posterior closure of the spine), heart abnormalities, and oro palatine cleft [15].

It should be noted that these various malformations can be observed without drug treatment, in children of bipolar mothers or not. There may also be an increased risk of developmental problems in a child whose mother received valproate during pregnancy, such as lower intellectual abilities, problems with speech and understanding, memory problems, autism spectrum disorders, and delay in walking and speaking [16]. To treat a bipolar woman, it may seem judicious to avoid valproate, however, the doctor may decide to use it, if there is no alternative or if the patient has been evaluated and is unlikely to respond to other treatments. He should then check that the patient is using reliable contraception and advise on the risks of taking the drug during pregnancy.

Valproate may be more effective as an antimanic rather than a prophylactic agent. Valproate might be a better choice in patients with many previous affective episodes/hospitalizations and psychiatric comorbidities [17].

Carbamazepine: Carbamazepine is usually only prescribed on the advice of a bipolar disorder specialist. To begin with, the dose will be low and then gradually increased. Beware of the combination with other medications, including the contraceptive pill. Blood tests to check liver and kidney function will be done when starting carbamazepine treatment and again after 6 months [18]. A complete blood count (NFS) should also be had at the start and after 6 months, and the patient's weight should also be monitored.

The antimanic properties of carbamazepine appear to be due to the depressant effect on the regeneration of dopamine and norepinephrine. Carbamazepine seems to act on different neurotransmitters probably responsible for its mood-regulating effect: Glutamate (decrease), GABA (increase), Dopamine (decrease in the number of D2 receptors), and serotonin (increase by inhibition of its reuptake) [19].

Oral absorption of carbamazepine depends on its galenic form. Maximum blood concentration peaks are obtained between 4 and 24 hours after a single tablet intake; the syrup makes it possible to reach this plasma peak more quickly. The plasma half-life is 36 h after a single dose; it decreases during repeated doses, due to auto-induction of hepatic enzymes, to be between 10 and 24 h. This half-life allows the prescription of a single daily dose [20]. The major metabolite, carbamazepine 10-11 epoxide, is active but is usually not assayed to monitor plasma levels.

Carbamazepine and oxycarbamazepine have antimanic efficacy, prevent manic relapses, and do not cause or worsen depression. There is no convincing data for either carbamazepine and oxycarbamazepine in the acute treatment of depression or the prevention of depressive relapses, and the duration of most controlled studies is insufficient to allow any conclusions about prophylactic efficacy over years [21].

Carbamazepine is used in children presenting with bipolar disorder but there are few open-label studies but not double-blind compared with placebo [22].

Lamotrigine: The use of lamotrigine has been authorized as a maintenance treatment (recurrence prevention treatment) for bipolar disorder. Lamotrigine is a viable and effective therapeutic strategy in the disease-modifying treatment of bipolar disorder, where a lower risk of recurrence than a placebo has been demonstrated [23]. Also, lamotrigine is found to be as effective as lithium.

The activity of lamotrigine is generally related to its action on voltage-gated channels (pre- and post-synaptic), stabilizing neuronal membranes. It also inhibits the release of glutamate during repeated potentials [24].

Plasma concentrations of lamotrigine are within a wide range (10 µmol/L to 60 µmol/L) since there is no relationship between these concentrations and toxicity or antiepileptic efficacy. It is therefore recommended to adjust the dosage according to the observed clinical efficacy and not to monitor plasma concentrations [25].

Due to adverse effects, particularly on the skin, the prescription of lamotrigine must follow a very specific schedule with an initial dosage in adults as monotherapy of 50 mg/d for 2 weeks, 100 mg for the following 2 weeks, and then if necessary increased from 50 mg to 100 mg every 1 to 2 weeks to obtain maintenance doses between 20 and 500 mg/day [26]. The doses of lamotrigine are generally lower in combination with valproic acid (100 mg/d to 200 mg/d) and the increase in doses is more gradual. The pharmacokinetics of this product is linear up to doses of 450 mg/d [27].

When lamotrigine is prescribed, it should usually start with a low dose, which will be gradually increased. It is essential to consult the attending physician immediately if a rash occurs. An annual checkup is required, but usually no further tests. Women taking birth control pills should talk to their medication about switching to another method of birth control.

Antipsychotic drugs

Antipsychotic drugs are often prescribed to treat manic episodes [28].

Aripiprazole: Results obtained with aripiprazole are particularly good since manic patients often show higher

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functional levels. It is particularly painful for them to take sedative and anticholinergic drugs, that is, drugs that could reduce their mental acuity [29]. Weight gain can also be an added burden for patients with bipolar disorder, as they are often more vigilant about their physical appearance. When sedation is desired, e.g., in the case of insomnia, it is a good idea to add a benzodiazepine or another sedative for the night but avoid excessive sedation during the day.

In terms of efficacy profile, atypical antipsychotics, including aripiprazole, are generally faster-acting than conventional mood stabilizers. One study showed that aripiprazole provided an earlier reduction in manic symptoms compared to lithium [30]. While aripiprazole was already different from placebo after two days in terms of efficacy, it took ten days with lithium. Manic patients need rapid control of their symptoms, which is why this difference is clinically significant. Another study showed that aripiprazole has a higher response rate overall than haloperidol. Significantly faster and better than mood stabilizers alone [31]. As monotherapy, aripiprazole works, faster or at least as effectively as conventional therapies [32]. Combination therapy with mood stabilizers shows superior efficacy compared to monotherapy. Since combination therapies are the general rule in the treatment of bipolar disorder, it is important to choose medications that do not complement each other and do not further accentuate the side effects. When, for example, an atypical is combined with a mood stabilizer that has a sedative effect or causes cognitive restrictions, a drug that does not have the same effects should be used. To this extent, the association of an antipsychotic causing fewer adverse effects, such as aripiprazole, makes it possible judiciously to optimize the efficacy and therapeutic observance and to reduce the number of side effects to a minimum [33].

Two clinical trials are evaluating the efficacy and safety of aripiprazole monotherapy over the long term. The first trial lasted six months [34], then it was extended to a total duration of two years [35]. After an acute phase trial lasting 3 weeks [36,37] or hospitalization for manic or mixed episodes, patients were included in an open phase called stabilization. Only euthymic patients (MADRS < 13 and YMRS < 10) lasting at least six weeks were included in the randomized, double-blind study phase versus placebo. The primary endpoint was the time before mood relapse. Among 633 eligible patients, 567 were included in the open stabilization phase and 206 patients responded to aripiprazole. But only 161 of them were included in the double-blind phase (77 for aripiprazole and 83 for the placebo). The authors do not detail the reasons for the 45 exclusions. Note that the article cites both 77 and 78 patients in the aripiprazole arm. Patients randomized to the placebo arm abruptly discontinued aripiprazole. Half of the patients on aripiprazole and 34% of the patients on placebo completed the 26-week trial. The average dose of aripiprazole at inclusion was 24.4 mg/day. The time to relapse for all episodes combined was significantly greater for aripiprazole (HR: 0.52; 95% CI [0.3; 0.91]; p = 0.02). The time to manic relapse was also in favor of aripiprazole but no difference was found for the time to depressive relapse. The symptomatic assessment was inconclusive. The authors report a significant difference in favor of aripiprazole for the evolution of YMRS. No difference was highlighted for the MADRS nor for the PANSS. Among patients who completed the 26-week trial, all patients receiving aripiprazole and 28 of 29 patients receiving placebo were eligible for inclusion in a 74-week extension study. Twelve patients completed the 100-week follow-up, with no difference between the two groups. The dose of aripiprazole was stable over the 100 weeks at an average of 23.6 mg/day. The results confirm those of the 26-week study, aripiprazole prolonged the time to mood relapse (HR: 0.53; 95% CI [0.32; 0.87]; p = 0.011) and that of manic relapse without modifying that of depressive relapse. A post-hoc analysis carried out by Muzina's team [38] evaluated the time to recurrence in patients known to have rapid cycles. The study of 28 patients confirmed the lengthening of the time to recurrence if aripiprazole was continued. The strong points of these clinical trials are the rigor of the protocol, double-blind execution, and randomization. Diagnoses as well as mood relapse were also assessed using standardized scales during long-term follow-ups. The stabilization period had a stricter definition than in other studies of the same type (YMRS < 10 for the aripiprazole study and < 13 for the previously cited quetiapine study). Its duration was longer than that of other studies. According to the authors, this methodology would allow the generalization of the results to a clinical population. Only the 26-week trial had a predefined objective for numbers and number of relapses; these objectives were achieved. The main purpose of the tests was respected and the result was positive. The limits are numerous. The number is the lowest of all comparable studies. The authors confirm that the enrichment of the protocol restricts generalization to patients responding to aripiprazole during a manic or mixed episode. Here the "enrichment ratio" is close to 4:1, this is the highest ratio found in antipsychotic studies published to date. The two groups were not comparable in every way since there was a significant difference regarding the type of acute episode. Mixedness represented 38% (n = 30) of the aripiprazole group and 22% (n = 18) of patients in the placebo group (p = 0.024), while mania represented 62% (n = 48) of the aripiprazole group versus 78%. (n = 65). The authors state without further details that this difference could not have influenced the results: "These differences were not expected to be significantly influential". According to exchanges between the Food and Drug Administration and the Otsuka laboratory published on the FDA website [39], this difference would not influence the results; however, the number was insufficient to assess the impact with satisfactory power. We regret the absence of multivariate analyses, which would have made it possible to adjust the results based on the type of index episode. Note also that the male/female population is unequal (sex ratio 1:2). This imbalance is not differential, so it would not be very limiting. Very few patients completed the study: at the twenty-sixth week only 12% of patients remained and only 1.3% completed the additional 74 weeks. No sample size was defined a priori for the 74-week trial, only twelve patients completed the protocol; this number appears to be very low for an evaluation of superiority. Intention-to-treat analyzes would have been beneficial. Like other studies, the clinical evaluation was inconclusive. The authors present an improvement in YMRS;

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however, this difference was only significant between weeks 18 and 26. Note also that even in responding patients, the effect of aripiprazole was insufficient to stem the worsening of manic symptoms over time. Thus, the change in the score over 100 weeks is +4.9 *vs.* +8.9 points, respectively for aripiprazole and placebo. The clinical benefit appears moderate. At 100 weeks, 38% of patients had received 15 mg/day and 62% had received 30 mg/day. Although this is not the objective of the study, the authors judge that these two dosages would be effective in preventing relapses. Note that these dosages are high and that they could not be reduced throughout the 2-year follow-up. All these limitations demonstrate the low validity of the studies by Keck, et al. However, in 2011, Tsai's team highlighted the significant representation of these studies in international literature [40]. One hundred and four publications cite these studies, all are in favor of the use of aripiprazole to prevent relapses but only 5% of them expose the methodological limits. According to this same team, the four limiting factors are the insufficient duration to evaluate the prevention of recurrences, the enrichment, the overestimation of the beneficial effects due to the abrupt transition to the placebo, and the low completion rate.

Two studies evaluated aripiprazole in combination with a mood stabilizer. They were both subsidized by the laboratory producing aripiprazole. In 2011, the team of Marcus published a trial evaluating the addition of aripiprazole after the failure of treatment with a mood regulator [41]. During an open phase, patients presenting with an acute manic episode or mixed received lithium or sodium valproate indifferently. In case of failure after two weeks of treatment with lithium or valproate (improvement in YMRS score less than 35% or score greater than 16), aripiprazole was added to mood-regulating monotherapy. The responding patients (YMRS and MADRS ≤ 12) had to be stabilized for 12 weeks to be randomized into two groups: maintenance or discontinuation of aripiprazole. Evaluation of effectiveness, estimated by the time to relapse, was then conducted double-blind for 52 weeks. The relapse was defined clinically and according to standardized scales (YMRS or MARDS > 16).

A total of 1270 patients were selected, 686 entered the open phase and 337 were included in the double-blind phase. The average dose of aripiprazole was around 15 mg/day. The addition of aripiprazole was associated with a reduction in the rate of relapses at 52 weeks (17% *vs.* 29% for aripiprazole and placebo respectively). The time to recurrence was significantly longer in the group receiving aripiprazole (HR = 0.54; 95% CI [0.33–0.89]). It was the same for the manic recurrence but no difference was demonstrated for depressive recurrence.

In 2013, Yathman's team published a post-hoc analysis evaluating the effectiveness of adjunct treatment according to the polarity of the index episode, manic or mixed [42]. The deadline for thymic recurrence was significantly prolonged in patients who had a manic episode but no difference was demonstrated in patients included during a mixed episode. The strong points of this study are the rigor of the protocol and the stabilization period of long-term and effective. The validity of the results is uncertain, the rate of patients known to carry out rapid cycles was much higher in the placebo group (10% *vs.* 3%). This inequality should not be neglected because the main criterion is the time for recurrence. Regardless of their treatment, it appears logical that patients presenting more than four episodes per year have a free interval shorter than the others. Thus, the main result of the study is partly a reflection of recurrence induced by the clinical subtype and not by the ineffectiveness of the placebo. Furthermore, the comparison of the recurrence rate according to the mood stabilizer used shows an absence of difference when valproate is combined with aripiprazole (18% and 19% respectively for aripiprazole and the placebo). Thus, the positive result is mainly induced by the difference in the recidivism rate in the "lithium" subgroup (16% for aripiprazole and 45% for placebo). Note the inequality in plasma lithium levels (73% to 87% of patients receiving aripiprazole had a lithium level between 0.6 and 1 mmol/l but only 40 to 76% of those receiving the placebo were in this fork). The underdosing of the placebo group may have widened the difference measured with aripiprazole. Woo's team published a clinical trial evaluating the effectiveness of aripiprazole in combination with sodium divalproate [43]. Patients who have suffered from a manic episode or mixed were included in the double-blind phase after a stabilization period of two weeks. Efficacy was evaluated over six months by the time of relapse. The protocol was therefore different since it evaluated the combination and the risk of relapse but the results are similar. Of the 83 randomized patients, no significant difference was demonstrated whatsoever for manic relapse, depressive relapse, or both.

Aripiprazole used as adjuvant treatment in patients resistant to mood stabilizers, would lengthen the time for non-depressive recurrences. Numerous methodological limitations highlight the risk of overestimation of the antimanic prophylactic effect. The association with valproate appears to be of no interest.

Olanzapine: Only one comparative and randomized trial received olanzapine in combination. Tohen's team assessed the effectiveness of adding olanzapine in patients with bipolar I disorder and a manic or mixed episode resistant to two weeks of mood stabilizer therapy (YMRS ≥ 15) [44]. After six weeks of treatment with dual therapy, patients in syndromic remission were randomized to the double-blind phase evaluating adjuvant treatment with a mood stabilizer versus placebo. The study assessed syndromic recurrence (assessed by DSM-IV criteria) and symptomatic recurrence (YMRS ≤ 12 and Harms ≤ 8) for any episode during a 12-month follow-up.

Of 160 eligible patients, 99 achieved syndromic remission and 68 symptomatic remissions with olanzapine + mood stabilizer dual therapy and were randomized to maintain olanzapine (N = 51) or discontinue in favor of placebo (N = 48). The average dose of olanzapine was 9 mg/day. Mean plasma levels were 0.76 mmol/l and 67 µg/ml respectively for lithium and valproate. No significant difference was found either for the delay or for the syndromic recurrence rate. In the 68 patients in symptomatic remission, the time to symptomatic recurrence

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was longer in the dual therapy group. The recurrence rate was not significantly different in the two groups. No significant difference was found in the rates or even the durations of manic recurrence. The same was true for the depressive side.

The protocol is suitable for superiority assessment. Rarely in this type of study, the number was calculated to achieve a power of 96% (for 168 patients). This trial is a continuation trial, there was no stabilization phase. The selected population in particular, are patients suffering from severe bipolar disorder (failure of a mood stabilizer, and then only half of them responded to the combination with olanzapine). Note also that they must have had two episodes in the past year, a definition that led to an over-representation of patients with the rapid cycle form. The lack of significance can be explained by the preventive ineffectiveness of the combination of a mood stabilizer with olanzapine; however, it is possible that the number is insufficient to highlight a small difference. The number defined a priori was not reached, the power achieved would therefore be 79%.

Note, however, that the only significant result was found in the most responsive patients during the acute episode (symptomatic and syndromic remission). This result demonstrates the impact of protocol enrichment. A surprising fact is not discussed by the author, the subgroup analysis shows an absence of significance in men.

Quetiapine: Only one clinical trial evaluates quetiapine as monotherapy in the prevention of relapses in all episodes. This multicenter trial [45] aims to compare the effectiveness and tolerance of maintaining quetiapine after obtaining a state of remission from an acute episode of type I bipolar disorder. The study included a 24-week open-label treatment phase during which patients were treated for manic, depressive, or mixed episodes. To be randomized in the blinded study, patients had to be in symptomatic remission (Young Mania Rating Scale (YMRS) and Montgomery-Åsberg depression rating scale (MADRS) < 12) at the twentieth week and have been stabilized for at least one year. month. At 24 weeks, the selected patients were randomized into three groups: maintenance of quetiapine (300 mg/d to 800 mg/d), switching to lithium (0.6-1.2 mEq/l) or a placebo. These patients were clinically evaluated for 104 weeks. The main criterion for judging effectiveness was the time before thymic recurrence. It was defined by thymic recurrence (YMRS or MADRS > 20) at two consecutive consultations, modification of therapies, hospitalization, or any event secondary to a thymic relapse. Tolerance was assessed by looking for clinical adverse effects, monitoring weight, and metabolic assessment. The methodology is complex, the analyzes are carried out on three different populations. The number defined a priori should make it possible to observe 600 thymic recurrences. Interim analyzes deemed positive led to the cessation of recruitment. Therefore, the results presented here come from three populations. The population of the interim analysis (n = 966), that of the intermediate ITT analysis (n = 730), and that of the ITT analysis at the end of recruitment (n = 1172). Indeed, recruitment was stopped due to a per-protocol analysis deemed positive.

Of the 2438 patients recruited during the open phase, only half (n = 1226) were included in the randomized phase. Intention-to-treat analyzes were performed on 1172 patients divided into three comparable groups. The average duration of exposure was 158 days for quetiapine, 83 days for lithium, and 74 days for the placebo. The mean quetiapine dose was 546 mg/day [standard deviation (SD) 173], and the mean plasma lithium levels were 0.63 mEq/L [SD 0.45]. Compared to placebo, continuation of quetiapine was associated with an increase in the time to recurrence for all episodes (HR 0.29; 95% CI [0.23; 0.38]; p < 0.0001; n = 1172), and for the time before manic or depressive recurrence. The evaluation of residual symptoms showed a significant difference in favor of maintaining quetiapine for mood symptoms (YMRS and MADRS) but not for positive psychotic symptoms assessed by the PANSS-P (Positive and Negative Syndrome Scale Positive Subscale). The study of cognitive functions using the MOS-Cog (Medical Outcome Study Cognitive Scale) and the trail-making test was discordant. Professional efficiency, assessed by the WPAI (Work Productivity and Activity Impairment Questionnaire) scale, did not show a significant difference between the two groups. The study of the time to thymic recurrence in the lithium and placebo groups was in favor of lithium (HR: 0.46; 95% CI [0.36; 0.59]; p < 0.0001; n = 1172). The analysis of the time to thymic recurrence for all episodes showed a significantly favorable difference for the continuation of quetiapine compared to a switch to lithium (HR: 0.66; 95% CI [0.49; 0.88]; p = 0.005). The strengths of this study are the large number of people and the rigor of the protocol. The comparative study is carried out double-blind, and the design as well as the statistical tests are adapted to an evaluation of superiority versus placebo.

The diagnoses are homogeneous and patients in acute depressive episodes were not excluded. Relapse was assessed according to standardized scales during follow-up defined a priori. The main objective is respected, and the result is positive. Unlike other comparable studies, the transition between quetiapine and placebo/lithium was gradual. This methodology makes it possible to avoid a bias of confusion between the relapse induced by abrupt withdrawal and the lack of effectiveness of the placebo or lithium. The limitations are numerous, the authors use the term “recidivism” even though the duration of stabilization is insufficient to speak of recidivism, whatever the definition used. Only half of the patients initially selected were included in the prevention phase. A certain inequality in terms of the type of mood episodes restricts the generalization of the results (1174 patients were in the manic phase, 554 in the mixed phase, and 710 suffered from a depressive episode). The average plasma lithium level was low, 37% of patients had a level below 0.6 mEq/l. Therefore, the authors emphasize that the interpretation of the quetiapine versus lithium results must be done with caution. The selection bias in favor of quetiapine is obvious. This bias is twofold, both induced by the inclusion criterion and the enrichment scheme. Finally, the exclusion criteria of the population limit the generalization of the results, with patients having had suicidal behavior or suffering from comorbidity being excluded. The difference in the time to relapse under quetiapine versus lithium for all episodes combined was not found for the time before depressive, manic,

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or mixed relapse. This result is not discussed by the authors but a lack of statistical power could be the explanation. The other explanation would be an underestimation of the effectiveness of lithium. Furthermore, this hypothesis is supported by the low median plasma lithium level. Two years after trial 144, Nolen and Weisler published a post-hoc analysis comparing the effectiveness of lithium versus placebo [46]. In patients treated with Lithium, the time before relapse for any episode was only prolonged in the event of lithium levels greater than 0.6mEq/l.

The Suppes team evaluated the effectiveness of quetiapine used in combination with a mood stabilizer to prevent thymic recurrences [47]. The methodology was similar to the previous ones; an open phase made it possible to select patients in the acute phase responders to the quetiapine + lithium or sodium valproate combination. These patients had to be euthymic (YMRS and MADRS ≤ 12) for 12 weeks to be randomized in order to maintain this dual therapy or to stop quetiapine. Effectiveness was assessed by the time to recurrence during 104 weeks. Among the 1953 patients selected, 628 were randomized (32.2%). The main reason for non-inclusion was the appearance of side effects. The initial population represented 623 patients; 176 patients completed follow-up (n = 110 and n = 66, for quetiapine and placebo, respectively). The average quetiapine dosage was 519 mg/day. Less than half (42.5%) of patients were treated with lithium at a mean plasma level of around 0.7 mEq/l. The plasma level average valproate was around 70 µg/ml. The time for thymic recurrence of all episodes combined was prolonged by the combination of quetiapine (HR: 0.32 95% CI [0.24 – 0.42]; $p < 0.0001$). The same was true for the time of manic and depressive recurrence. The study carried out by Vieta (essay 126) is contemporary with that of Suppes [48].

The evaluation of the effectiveness of quetiapine used in combination with a mood stabilizer was carried out according to a methodology perfectly superimposable to test 127. The results with the intention to treat included 703 patients among the 1461 previously selected. The combination of mood stabilizer and quetiapine prolonged the time to thymic recurrence (HR: 0.28; 95% CI [0.21; 0.37]; $p < 0.001$). The same was true for the delays in manic or depressive recurrence.

The advantages of these studies are certain, they are suitable for an estimation of superiority and an assessment of recidivism. The workforce was very large. The term "recurrence" is used to assess recidivism. Even if the lithium levels were slightly low, they were higher than those used in comparable tests. Unlike Marcus's study evaluating aripiprazole, the results were not influenced by the index episode or the type of dual mood-regulating therapy. In order to limit the impact of the effect linked to withdrawal, analyzes censoring recurrence in the first four weeks were carried out, and they confirmed the results. The limits are few in number but in no way discussed by Suppes. Note that thymic recurrence is defined by classic criteria such as syndromic recurrence, therapeutic modification, and hospitalization; however, the scores necessary to define the symptomatic recurrence were higher than in other studies (YMRS or MADRS ≥ 20). No measures of quality of life or residual symptoms were assessed. Moreover, the evaluation of recurrences tends to overestimate the effect of antipsychotics. In fact, dual therapy is a second-line treatment; however, the pre-inclusion phase does not assess resistance to monotherapy. Vieta highlights the effect of enrichment and the absence of a specific evaluation of mixed recidivism.

On the other hand, a randomized study evaluated the efficacy and safety of lithium or placebo as an add-on to quetiapine XR in adult patients with manic or mixed symptoms of bipolar I disorder [49]. In this 6-week, double-blind study adult patients with DSM-IV-TR-diagnosed bipolar I disorder (current episode manic or mixed), a Young Mania Rating Scale (YMRS) total score ≥ 20, and score ≥ 4 on two of four core YMRS items were administered quetiapine XR (400 to 800 mg/day) and randomly assigned to receive add-on lithium (600 to 1,800 mg/day) or placebo. The primary efficacy endpoint was a change in the YMRS total score from baseline to day 43, analyzed using a mixed-model for repeated measures (MMRM) approach. Secondary efficacy and safety endpoints were also measured. Rating scales were administered by trained staff. Three hundred fifty-six patients treated with quetiapine XR were randomized to add-on lithium (n = 173) or placebo (n = 183). Two hundred ninety-one patients (81.7%) completed the study. At day 43, the least squares mean change in YMRS total score was -22.8 for add-on lithium and -20.1 for add-on placebo, a statistically significant treatment group difference of -2.69 ($p < 0.001$). On secondary measures, add-on lithium was associated with significant improvements in response, remission, illness severity, and overall illness versus add-on placebo ($p < 0.05$). The number needed to treat was 9.1 for response and 7.9 for remission for add-on lithium compared with add-on placebo. Lithium in combination with quetiapine XR was generally well tolerated, with a similar profile to quetiapine XR in combination with placebo. The addition of lithium to quetiapine XR therapy was associated with significantly greater efficacy than placebo as an add-on and was generally well tolerated in patients with acute bipolar I mania.

The particular psychopharmacological action profile of quetiapine and its active metabolite norquetiapine represents an advantage in the treatment of acute bipolar depression [50].

Mixed states

Some people with bipolar disorder experience simultaneous manic and depressive symptoms. This is called a mixed episode. For example, a person experiencing a mixed episode may think and speak very quickly. At the same time, she may feel intense anxiety and have suicidal thoughts. Mixed episodes are difficult to diagnose and very painful for the individual. To do this, a scale was developed, the GT-MSRS [51]. The management of mixed states is challenging with atypical antipsychotics, newer anticonvulsants, and electroconvulsive therapy emerging as the foremost treatment options. In conclusion, while progress has been made in the neurobiological understanding of mixed states, the currently available therapeutic modalities have only

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shown limited effectiveness [52]. There are no good clinical trials to prove the efficacy of one treatment over another, the clinician tries several drugs depending on one experience.

Conclusion

The treatments most often prescribed for bipolar disorder are called mood stabilizers. These treatments reduce the frequency, duration, and intensity of episodes and improve the quality of free intervals. Their effectiveness can only be assessed after at least 6 months of treatment. For some, treatment must be maintained for life. An interruption of treatment cannot generally be considered before a period of stability of at least 2 years and must be carried out very gradually under medical supervision [53].

All these considerations mean that there are few well-conducted and well-documented clinical trials. Many molecules have had difficulty obtaining marketing authorization for the prevention of relapses. This is the case of lamotrigine which is now one of the most used long-term products. The same will probably be true for aripiprazole and quetiapine.

Finally, the most important thing is that the molecules on the market have not been studied in bipolar disorder type 2, which leads to extrapolating the results obtained in bipolar disorder type 1. We can easily understand why, in the measure of lithium the ancestor of mood stabilizers began to be used empirically in the 2 types of bipolar disorders. Then it was long considered that it should be reserved for bipolar 1 disorder while valproate was more effective in bipolar 2 disorder, yet BP 2 offers less clinical consensus than BP1.

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