REVIEW

State of the Art: Treatment of Bipolar Disorders

Emanuel Severus, Nadine Schaaff, & Hans-Jürgen Möller

Department of Psychiatry, University of Munich, Munich, Bavaria, Germany

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Correspondence

Emanuel Severus, M.D., Department of Psychiatry, University of Munich, Nussbaumstrasse 7, 80336 Munich, Germany.
Tel.: 0049 89 5160 5755;
Fax: 0049 89 5160 5188;
E-mail: Emanuel.Severus@med.uni-muenchen.de
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SUMMARY

Bipolar disorders are lifelong lasting affective disorders, with an episodic course of the illness in most cases. The lifetime prevalence is around 2–5%, the illness usually appears in early adulthood and causes significant impairment in psychosocial functioning. This is a selective review focusing on recent developments and issues of interest in the psychopharmacological treatment of bipolar disorders. It is based primarily on the results of adequately powered, randomised, controlled trials (RCTs). These studies were systematically retrieved by means of a Medline search. The past 10 years have led to a broadening of the psychopharmacological treatment options for bipolar disorders. The proof of efficacy for the combination of fluoxetine/olanzapine as well as quetiapine in the acute treatment of bipolar I depression were important steps. While lithium remains the gold standard in the maintenance treatment of bipolar disorders, valproate, olanzapine, lamotrigine, aripiprazole, and quetiapine have been shown efficacious for this indication, with quetiapine possessing the broadest approval status of all drugs for the different treatment phases of this illness. Despite this progress there remains a huge demand regarding new compounds for nearly every area in the psychopharmacological treatment of bipolar disorders. In addition new methodological approaches regarding the proof of effectiveness in clinical practice are urgently needed.

Introduction

The following review deals primarily with the psychopharmacological treatment of bipolar disorders. It is a selective review focusing on recent developments and issues of interest. It is based primarily on the results of adequately powered, randomised, controlled trials (RCTs). Despite the fact, that these studies may suffer from limited external validity they represent the only established method so far to find out whether a drug has beneficial effects beyond those associated with the belief of receiving a potentially efficacious drug (placebo).

Bipolar disorders are lifelong lasting affective disorders, with an episodic course of the illness in most cases. The lifetime prevalence is around 2–5%, dependent on the diagnostic criteria used, the sex ratio is 1 : 1. Bipolar disorders can be divided into Bipolar I Disorder (at least 1 manic or mixed episode) and Bipolar II Disorder (at least one hypomanic and one depressive episode). The illness usually appears in early adulthood, depressive symptoms, and episodes tend to dominate the course of the illness. Significant impairment is the rule rather than the exception resulting in significant economic consequences, for the individual as well as the society. Psychiatric comorbidity occurs frequently (anxiety disorders, substance disorders, and personality disorders). Furthermore the risk for dementia and cardiovascular morbidity and mortality is elevated [1].

Methods and Results of Recent Approval-Seeking Studies in the Long-Term Treatment of Bipolar Disorders

The treatment of bipolar disorders is traditionally divided into acute treatment, continuation treatment (continuation of the acute treatment to prevent relapse as the underlying episode is still present), and prophylactic treatment (prevention of new episodes/recurrences, after the index episode had come to an end). Sometimes continuation treatment and prophylactic treatment are subsumed under the term “long-term treatment” [2]. In recent approval-seeking long-term treatment studies the term “maintenance treatment” is often used. Maintenance treatment usually starts during continuation treatment and expands into prophylactic treatment, covering a variable number of months of the latter treatment period, dependent on the individual study. Subjects included into these studies had responded to the drug to be tested during a preceding open-label treatment phase for an acute affective episode before being randomized to the double-blind, placebo-controlled treatment phase. Alternatively, subjects who responded for an acute affective episode with another drug are switched to the drug of interest during open-label continuation treatment—and are only included into the double-blind treatment phase if response is maintained for a period of several weeks on the drug to

be tested. Therefore those studies are referred to as enriched studies as the study samples are enriched with acute treatment—responders to the drug subsequently tested for efficacy during long-term treatment. The reason for this approach is based on the observation that acute response seems to predict long-term efficacy. This is at least suggested by the results of the approval-seeking study for valproate published in 2000 [3,4]. In this study only those subjects who responded to valproate during the acute treatment for a manic episode and continued on this treatment had a longer time to a new episode compared to those who responded to valproate during the acute treatment and were randomized to lithium during the following double-blind treatment phase [3,4].

Following the valproate trial, this study design was successfully implemented at the subsequent approval-seeking studies for lamotrigine [5,6], olanzapine [7], aripiprazole [8,9] and quetiapine [10,11], with time to a new affective episode as the primary outcome parameter. However there are differences regarding the range of efficacy between the aforementioned drugs. For example, lamotrigine [5,6] has only been shown to be efficacious in the prevention of depressive, but not manic episodes, whereas aripiprazole [8,9] has been shown to be effective in the prevention of manic, but not depressive episodes. In contrast, olanzapine [7] and quetiapine [10,11] have been shown to be efficacious in the prevention of both mania and depression.

What is the impact of these findings for the use in clinical practice? In the first place this means, that these drugs, strictly speaking, have only been shown to be efficacious in patients who had responded to the same drug for the acute treatment of an antecedent affective episode—and therefore should, in principle, only be used in this context [12]. Second, the drug intended for the long-term treatment should only be used acutely for an affective episode for which it has been proven efficacious—and has (ideally) received approval for. For example, aripiprazole [13,14], valproic acid [15], and olanzapine [16] have been clearly shown efficacious in the acute treatment of a manic, but not depressive episode, whereas lamotrigine has demonstrated some efficacy in the acute treatment of a depressive, but not manic episode [17,18]. In contrast, quetiapine is approved for the acute treatment of both manic and depressive episodes [19]—and therefore can be used in the most diverse clinical circumstances for the long-term treatment of bipolar disorders.

What is the position of lithium, the hitherto existing gold-standard in the long-term treatment of bipolar disorders, compared to the aforementioned newer substances [20]? It seems crucial to point to the fact that the proof of efficacy of lithium, in contrast to the aforementioned drugs, has been demonstrated in a non lithium-enriched design, that is, in patients without antecedent acute response to lithium for an affective episode [5,6]. In addition the proof of efficacy was made in earlier studies with a less sensitive methodology than used nowadays (number of affective episodes in contrast to time to a new affective episode)—what makes it more difficult to demonstrate the efficacy of a drug [21]. Furthermore, lithium represents the only drug so far which was shown superior to another approved substance for the long-term treatment of bipolar disorders in a well balanced study design [22]. Therefore, even today, lithium holds a unique position in the long-

term treatment of bipolar disorders. The only study so far, still unpublished, comparing lithium with quetiapine (SPARCLE) demonstrated both substances to be superior to placebo. In addition quetiapine was superior to lithium in the prevention of depressive episodes—in patients who responded to quetiapine for the acute treatment for an acute episode—which were approximately 50% of those openly treated with quetiapine. Therefore this result cannot be fully counted when it comes to head-to-head comparisons between approved drugs in this indication.

Regarding the other drugs approved for maintenance treatment of bipolar disorders it appears that lithium and lamotrigine [5,6,23] and lithium and olanzapine [24] are similarly efficacious, with some advantage of lithium compared to lamotrigine with regard to manic episodes (and vice versa) [5,6] as well as of olanzapine compared to lithium with regard to manic episodes (and vice versa) [24]. A *post hoc* analysis of the latter study demonstrated that previous use of lithium was a risk factor for depressive episodes in this study [25]. As 70.8% of the study participants, who were randomized to lithium, had taken lithium in the past, the prophylactic efficacy of lithium might have been even more robust if more study participants had been lithium-naïve at the time of entry into the study. It is noteworthy that a past history of lithium intolerance or lack of efficacy of lithium was an exclusion criterion in this study. Interestingly, similar percentages of previous lithium use were reported by the other recent approval-seeking studies in the last few years where lithium served as a comparator [5,6].

Antidepressants in the Acute and Long-Term Treatment of Bipolar Disorders

What about the efficacy and risk of switch into a hypomanic or manic episode of antidepressants in the acute and long-term treatment of bipolar disorders? The available data for answering this question appear, at first sight, controversial, in particular with regard to the first issue. There are three large studies available meeting the methodological requirements (adequately powered, randomized, double-blind, and controlled trial) necessary to answer these questions [26–28]. However it was only in one study that the power analysis was targeted at the question of interest to us [27]. Out of these three studies the antidepressants were clearly efficacious in one study [26], in the other two studies the antidepressants did not separate from placebo [27,28]. There are several putative candidates, which may help explain these discrepant results (i.e., disparate antidepressants, disparate dosing schedules, monotherapy versus combination therapy with disparate mood stabilizers, and percentage of chronically depressed patients). Keeping in mind, that the proof of efficacy for any specific drug is always dependent on the individual setting of the trial it seems prudent to take a closer look at the study modalities [29]. The optimal study design for interpreting the efficacy data of a new compound would consist of three adequately and comparably powered treatment arms. The three treatment arms a study participant could be randomized to would consist of the new compound (monotherapy), an approved standard compound for this indication and a placebo. This study design has several advantages. In case the new compound does not significantly

separate from placebo it allows to differentiate between a “failed” study (the comparator does not separate from placebo either, therefore reasons immanent in the study design probably account for the negative outcome) and a negative study (the standard comparator significantly separates from placebo, but not the new compound to be tested). In addition, in case the new compound significantly separates from placebo, this study design allows to get a preliminary idea of the efficacy of the new compound, in comparison to the standard approved drug, on condition that the study was adequately powered to address this question. With regard to the issue interesting to us these requirements pose a problem regarding two aspects. At first there has not been a standard comparator approved for bipolar depression until very recently (nowadays quetiapine represents such a standard comparator). At second there is a broad consensus in the major treatment guidelines that an antidepressant should only be used in combination with an (prophylactically) efficacious compound against manic episodes, which does not go along with an increased probability for depressive symptoms/episodes (“mood stabilizer”) [30–32]. Under these circumstances the study by Sachs *et al.* provides the least information with regard to the efficacy of antidepressants in bipolar depression [27]. In this study the antidepressants did not significantly separate from placebo—however no standard comparator was used as a third treatment arm [27]. Taking a close look at the study methodology there are some characteristics, which might indicate that this study was in fact a “failed” study. For example, in contrast to the other two studies, this study was a so-called “effectiveness”/“real world” study. Approximately 2/3 of all patients, in both intervention groups, received psychotherapy in addition to the psychopharmacological intervention. Furthermore it is noteworthy that the treatment group which received an antidepressant in addition to the “mood-stabilizer” did (numerically) worse than the group receiving the “mood stabilizer” alone. This is a phenomenon which has not been encountered so far in trials of antidepressants in bipolar depression [33]. One possible reason for this phenomenon might be rooted in the composition of the study sample: 2 689 potentially eligible patients were screened, however only 366 were finally randomized to one of the two treatment arms. Two of the three reasons the authors put forward to account for the fact that only a small proportion of those potentially eligible were finally randomized into the study were the fact that potential study participants were not willing to taper off an antidepressant present at screening as well as running the risk of not receiving an antidepressant, but only a mood stabilizer during the trial [34–36]. Consequently, it is possible that only those subjects were included into the study who did not experience any benefit from antidepressants in the past (e.g., chronically depressed, potentially treatment-refractory patients) as well as those who did well on mood stabilizers alone. Thereby a potential negative bias may have been introduced regarding antidepressants, and a positive regarding “mood stabilizers.”

The other two studies do not classify for the category “failed studies.” In one of these studies the antidepressant clearly separated from placebo [26], in the other study the antidepressant did not separate from placebo—however quetiapine did. Consequently the latter study has to be counted as a negative study [28]. How can these discrepant results be explained? Possible rea-

sons may be found in the choice of the antidepressant (paroxetine versus fluoxetine), monotherapy (paroxetine) versus combination treatment (fluoxetine/olanzapine) with a prophylactically efficacious antimanic and antidepressant agent (olanzapine), in the dosing regimen used (in the case of fluoxetine/olanzapine flexible dosing strategy, with the possibility of dose escalation, versus paroxetine, 20 mg continuously) and in the composition of the study sample (“Bipolar I” versus “Bipolar I and Bipolar II”). It should be stressed that the proof of efficacy of the combination of fluoxetine/olanzapine was quite impressive (the combination of fluoxetine/olanzapine was not only superior compared to placebo, but also to olanzapine—which itself was superior to placebo) and included the core symptoms of depression. In addition the fluoxetine/olanzapine treatment arm had only been included for exploratory reasons—and was therefore clearly underpowered—which in turn makes it more difficult to proof efficacy.

In conclusion, the available data indicate that fluoxetine [37], but presumably other selective serotonin reuptake inhibitors (SSRIs) as well, at least in combination with an acute but also prophylactically antimanic and antidepressive drug (olanzapine, lithium, presumably quetiapine) are efficacious in the acute treatment of bipolar I depression, at dosages traditionally used in the treatment of unipolar major depression [38–40]. This scenario may differ for mixed depression and depressive episodes in the course of (ultra) rapid cycling. In this context antidepressants should be used very cautiously—and, in fact, it may be a better choice to refrain from the use of any antidepressant and to taper off any antidepressant if present [41,42]. Besides SSRIs several small studies point to the efficacy of tranylcypromine, even in cases of treatment resistance, with little risk of switch to the opposite pole [33,43–45]. In general regarding the risk of switch to the opposite pole much more research is needed. The current data indicate that combination treatment with drugs which are efficacious in the acute and long-term treatment of manic episodes seem to diminish that risk whereas tricyclics and venlafaxine and reboxetine seem to increase it (without being associated with superior antidepressant efficacy), whereas SSRIs seem to have a low risk [46,47]. In addition, on an individual level, there may exist large differences with regard to the risk of switching [48]. Therefore it is obligatory to take a diligent history of the previous treatment history.

Regarding the efficacy of modern antidepressants in the long-term treatment of bipolar depression the first pilot study with an “enriched” design has recently been published, imitating the methodology used for the recent approval-seeking studies in the long-term treatment of bipolar disorders [49]. In contrast to those, but comparable with the study by Sachs *et al.*, examining the efficacy of antidepressants in the acute treatment of bipolar depression, this study is part of the STEP-BD trials—and therefore an “effectiveness/real world study,” with the inherent advantages (with regard to external validity) and disadvantages (e.g., “background noise”) associated with this type of studies. Another prominent feature of this trial is the trial’s methodology, that is, this study is a randomised, open-label study. Patients with bipolar I and bipolar II depression, who experienced recovery on combined treatment with an antidepressant (SSRI, venlafaxine, bupropion) and a mood stabilizer over at least 8 weeks’ duration were included

into this trial. Seventy patients were randomised, 32 continued on the antidepressant, in 38 cases it was tapered off. Regarding the primary outcome (mean change on the depressive subscale of the CMF) at 12 months there was only a trend in favor of the antidepressant group ($P = 0.06$). However there was a significant difference in favor of the group, which continued with the antidepressant regarding the outcome "time to first depressive episode." This is noteworthy as "time to a new episode" was the primary outcome criterion in the afore-mentioned other approval-seeking studies. Therefore this study is compatible with the assumption that a combination like fluoxetine/olanzapine, which was superior to olanzapine as well as placebo in the acute treatment of bipolar I depression, may prove efficacious in the long-term treatment as well, if used in the context of an adequately powered randomised double-blind, placebo-controlled enriched efficacy study design. Consequently a study like this (or similar studies) should be definitely conducted to be able to give clearer recommendations regarding this issue.

Summary, Limitations, and Outlook

Fortunately the past 10 years have led to a broadening of the psychopharmacological treatment options. The proof of efficacy for the combination of fluoxetine/olanzapine as well as quetiapine in the acute treatment of bipolar I depression were important steps. Quetiapine has the broadest approval status of all drugs licensed for the treatment of bipolar disorders. Nevertheless quetiapine remains an (atypical) antipsychotic associated with the characteristic side effect profile for this class of drugs, even if the intensity and frequency, for example, regarding extrapyramidal motor symptoms (EPMS), is rather favorable compared to other members of this family [50]. Another important result of the studies of the last few years was the impressive confirmation of the efficacy of lithium in the long-term treatment of bipolar disorders so that even nowadays lithium remains the gold standard for this indication.

Despite this progress there remains a huge demand regarding new compounds for nearly every area in the psychopharmacological treatment of bipolar disorders. From a methodological point

of view, in particular when it comes to a head-to-head comparison between a new compound and a drug already approved for this indication, it seems essential to make sure that a fair contest between those compounds is granted. This would imply, among other issues, that study participants are ideally naive to both substances [25], that a power analysis results in comparable conditions for both substances, and in case an enriched design is used, that it is applied to both compounds in a balanced way [24].

During the last few years several effectiveness trials have been conducted, for example, in the context of STEP-BD, to have data with higher external validity than those, which typically result from phase III studies. While there are good reasons for this procedure it remains true that these studies are generally not an ideal tool to answer the question whether a new compound is potentially efficacious in the treatment of bipolar disorders. In addition, the external validity of those studies may be compromised if the study sample is not representative of the entire population of patients with bipolar disorders. Furthermore, in the case of double-blind, placebo-controlled trials, randomization, blinding, and placebo control may present an obstacle for high external validity. It remains to be seen whether the use of Marginal Structural Models may result in more valid findings [25,51–53].

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Conflict of Interest

Emanuel Severus is on the speakership bureaus of AstraZeneca and Eli Lilly and Company.

Nadine Schaaff: none to declare.

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