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REVIEW

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Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice?

A conceptual review

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Abstract This conceptual review summarises the results of relevant studies on antidepressants, mood stabilisers such as lithium and anticonvulsants, and second generation antipsychotics in the indication of bipolar depression. Based on methodological and clinical considerations, the position of antidepressants and the possible alternatives in this indication are reviewed very carefully. In addition the regulatory requirements for licensing a drug for the indication 'short-term treatment of bipolar depression' are described.

Key words mood stabilizers · lamotrigine · acute bipolar depression · antidepressants · second generation antipsychotics

Introduction

In some European countries, antidepressants have a long tradition of being the drugs of first choice in the treatment of acute bipolar depression. This tradition still has a strong impact on treatment decisions in routine care (Kasper et al. 1999; Walden et al. 1999). However, particularly in US-American and Canadian psychiatry there is a strong tendency generally to avoid antidepressants in bipolar depression and to rather treat even severe depression with mood stabilisers (lithium, anticonvulsants) in monotherapy. This position is also underlined by the fact that in the case of co-medication with mood stabilisers and antidepressants it is seen to be mandatory to withdraw the antidepressants as early as possible after sufficient antidepressive response has been obtained (Sachs et al. 2000a). The achievement of remission with antidepressants, which is nowadays the primary goal in the acute treatment of unipolar depression (Hirschfeld et al. 2002; Keller 2003), is apparently not considered to be a necessary criterion before discontinuing treatment with antidepressants. This general tendency aimed towards the avoidance of antidepressants in the treatment of acute bipolar depression has been expressed, of course with certain modifications, in several expert opinions, consensus papers and guidelines (Bauer et al. 1999; Frances et al. 1996, 1998; Hirschfeld et al. 1994; Kusumakar et al. 1997; Motohashi 1999; Sachs 1996; Yatham et al. 1997). The so-called European Algorithm Project (based on the consensus of some European experts) also reflected this tendency (Goodwin and Nolen 1997).

The recommendations published in the different papers and guidelines are not identical but they follow a similar general direction: avoid the use of antidepressants in mild, possibly also in moderate or even severe depression, and in general only use antidepressants if they are "clinically necessary", whatever the latter term, which is not defined or operationalised in any way, means. Apparently, in this clinical decision-making the hypothesised risk of mania and risk of rapid cycling induced by antidepressants has been given more weight in comparison to the risks associated with insufficient antidepressive treatment, which include suicidal acts and chronicity of depressive symptoms, among others (Angst et al. 2005). In unipolar depression, insufficient treatment with antidepressants has been identified as the major risk factor for suicide (Andersen et al. 2001) and chronicity of depressive symptoms. As a consequence, the traditional and current state of the art, i. e. the prescription of antidepressants, aims to reduce as far as possible the symptoms of depression in unipolar patients, in order to avoid the risk of chronicity and suicidality (Hirschfeld et al. 2002; Keller 2003). It seems principally meaningful to transfer this treatment concept to

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the treatment of acute bipolar depression, i. e. to prescribe the most powerful antidepressive treatment (Bottlender et al. 2000). Based on these considerations the traditional view that antidepressants play an important, if not central role in the treatment of acute bipolar depression seems well justified, based on the whole body of available evidence (Möller and Grunze 2000). This position is stated in the acute bipolar depression treatment guideline paper by the World Federation of Societies of Biological Psychiatry (Grunze et al. 2002) as well as in the respective guideline paper of the British Association for Psychopharmacology (Goodwin 2003), among others. The "Expert Consensus Guideline on Medication Treatment of Bipolar Disorder" (Sachs et al. 2000b), which summarises the views of prominent North American experts, is also much more open towards the use of antidepressants than the respective APA guideline (American Psychiatric Association 2002).

This not only appears meaningful with respect to a fair balance between clinical benefits and the risks associated with the administration of antidepressants versus the benefits and risks of monotherapy with mood stabilisers, but also from a theoretical point of view, which considers the efficacy of psychopharmaceuticals as syndrome- and not illness-oriented. This syndrome-oriented concept, which was first proposed by Freyhan (1957), means, among others, that antidepressants are indicated in all kinds of depressive syndromes, independent of whether the origin is functional, endogenous, neurotic or organic, or whether they are unipolar or bipolar. The implication of this syndromatic approach is that a drug which has proven efficacy in unipolar depression is hypothetically also effective in treating depressions of other aetiopathogenetic backgrounds. It is noteworthy in this context that the guideline paper by the British Association of Psychopharmacology on the treatment of bipolar disorder (Goodwin 2003) apparently follows such a syndromatic approach, at least in the context of refractory bipolar depression, where it recommends the same procedure as for refractory unipolar depression. It is also noteworthy that DSM-IV uses the term 'major depressive episode' in the context of both unipolar and bipolar affective disorders; the entity 'acute bipolar depression' as a separate entity does not exist. For example, in DSM-IV 'bipolar I disorder' is characterised by one or more manic or mixed episodes, usually accompanied by major depressive episodes, (American Psychiatric Association (APA) 1994, page 317). A similar definition is used for bipolar II disorder. Furthermore, most antidepressants are licensed for the indication 'depression' or 'major depressive episode' in general.

Two recent publications of a study by the Stanley Network (Altshuler et al. 2001, 2003) suggest that antidepressants even have their place, in combination with a mood stabiliser, in the continuation treatment of bipolar depression and result in a better outcome. Although this study follows a naturalistic design, the results should not be ignored. The fact that in the long-term course of bipolar affective disorders the average duration of depressive symptoms is much longer than the duration of manic symptoms, and that the clinical and social consequences seem to be much more severe (Judd et al. 2002), should attract a great deal of attention. In this context is should also be considered that apparently the currently applied mood stabilisers – lithium and anticonvulsants such as valproate and carbamazepine – are more effective in preventing manic episodes than in preventing depressive episodes (Severus et al. 2005). Only lamotrigine has a special focus on relapse prevention of depressive episodes of bipolar disorders (McElroy et al. 2004).

Hopefully, the final balance between the two antagonistic positions mentioned above will eventually be decided on the basis of the growing amount of data from new studies on the traditional mood stabilisers and/or studies on new mood stabilisers from the group of anticonvulsants or other psychopharmacological agents (e. g. second generation antipsychotics) as to whether they can demonstrate antidepressive efficacy of the same degree as antidepressants. Thus the appearance and evaluation of lamotrigine in this field, together with the publication of some other relevant trials, seems a suitable time to re-evaluate the situation.

This paper is rather a conceptual or critical than a systematic review. This means that it focuses on the most relevant studies and discusses them in the light of careful methodological considerations and in the general frame of conceptual considerations of the pros and cons of the replacement of antidepressants with other drugs in the indication acute bipolar depression. This differs from a systematic review in that not all papers are described in detail.

The efficacy of antidepressants in acute bipolar depression as the standard of comparison

Several experts, consensus papers and guidelines recommend mood stabilisers as the treatment of first choice in acute bipolar depression. This recommendation has to be questioned as long as there is no definite proof that these mood stabilisers have antidepressive efficacy in acute bipolar and/or unipolar depression compared to placebo, and that this efficacy is comparable to the antidepressive efficacy of traditional or modern antidepressants.

Although not the main focus of this paper, its starting position is that antidepressants are as effective in bipolar as in unipolar depression, although for special reasons related to the history of the clinical development of antidepressants this has not been proven formally. In the early days of antidepressant trials, i. e. the efficacy evaluation of most tricyclic antidepressants, both unipolar and bipolar depressive patients were recruited for the phase III trials, based on the syndromatic approach and without differentiation related to the efficacy outcome. Later on, when selective serotonin reup-

take inhibitors and other modern antidepressants were being evaluated, to avoid the risk of mania, bipolar patients were excluded from the trials required for drug approval. Only a few randomised studies have been performed to test the efficacy of antidepressants in the treatment of acute bipolar depression (Table 1). However, the sample size in all of these studies was very small and thus the risk of a β-error problem very high. Nevertheless, some of these studies demonstrated efficacy (Möller and Grunze 2000). A recent meta-analysis (Gijsman et al. 2004) underlined that there is only limited evidence from specialised studies on antidepressants in the field of acute bipolar disorder. On the other side it came to the conclusion that even based on the limited number of studies – 12 randomised trials with a total of 1088 patients were included in the meta-analysis, whereby only five trials were placebo-controlled – that "antidepressants are effective in the short-term treatment of bipolar depression" (Gijsman et al. 2004, page 1537) (Fig. 1).

Beside efficacy in terms of response rates, clinical usefulness is a key issue for any treatment choice. This means that efficacy and tolerability have to be well balanced. In a double-blind study by Young et al. (2000) 27 patients were randomly assigned to groups that either received combination treatment of one mood stabiliser (lithium or valproate) and paroxetine or a combined treatment with these two mood stabilisers. To be eligible for the study, patients had to have been treated with either lithium or valproate in therapeutic blood serum

Table 1 Characteristics of randomised, controlled trials of antidepressants for bipolar depression (Gijsman et al. 2004)

	N	Country of study	Drug comparison	Concurrent medication
Antidepressant versus placebo				
Tohen et al. 2003	456	13 countries	Fluoxetine, placebo	100% olanzapine
Nemeroff et al. 2001	117	United States	Paroxetine, imipramine, placebo	100% lithium
Cohn et al. 1989	89	United States	Fluoxetine, imipramine, placebo	25% lithium
Himmelhoch et al. 1982	59 (29 with bipolar disorder)	United States	Tranylcypromine, placebo	None
Mendlewicz and Youdim 1980	58 (34 with bipolar disorder)	Belgium	Deprenyl, placebo	None
Antidepressant versus antidepressant				
Silverstone 2001	156	Australia, Africa, Europe	Imipramine, moclobemide	40–45% lithium, 6% carbamazepine, 1% sodium valproate
Sachs et al. 1994	15	United States	Desipramine, bupropion	100% lithium, sodium valproate, or carbamazepine
Himmelhoch et al. 1991	56	United States	Imipramine, tranylcypromine	None
De Wilde and Doogan 1982	9	Belgium	Fluvoxamine, clomipramine	None
Antidepressant versus other medicine				
Young et al. 2000	27	Canada	Paroxetine, mood stabiliser	100% lithium or sodium valproate
Grossman et al. 1999	16	United States	Idazoxan, bupropion	> 0% lithium
Bocchetta et al. 1993	30	Italy	Amitriptyline, sulpiride	100% lithium

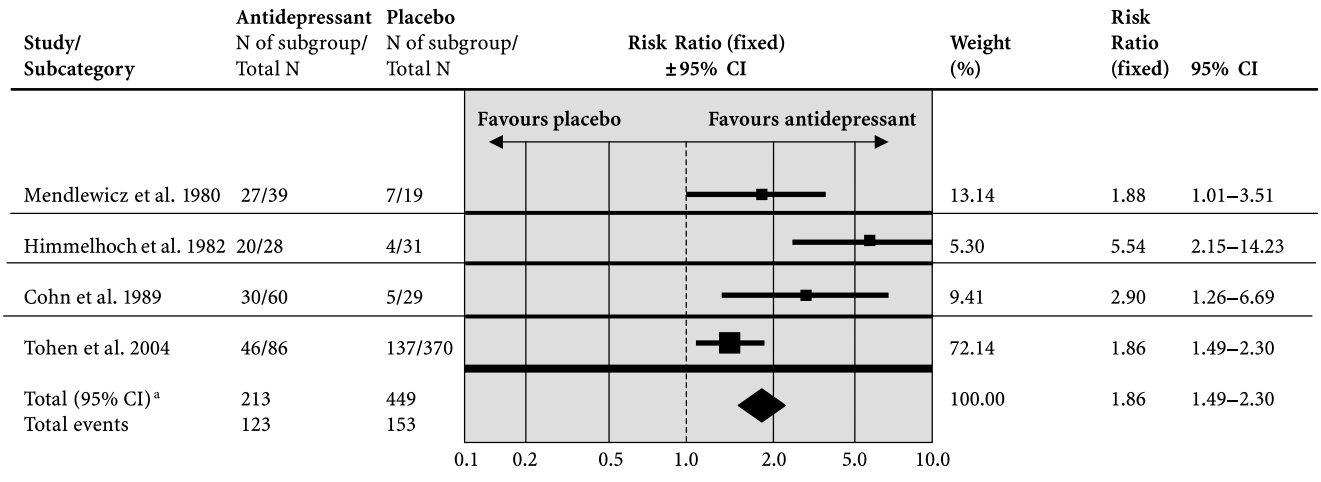

Fig. 1 Fixed-effect model of clinical response in randomised, controlled trials of antidepressants versus placebo for the treatment of bipolar depression (Gijsman et al. 2004). [a] Significance test for heterogeneity ($\chi^2 = 10.51$, df = 3, p = 0.01; $I^2 = 71.4\%$). Significance test for overall effect (z = 5.60, p < 0.00001).

concentrations for at least 6 months prior to the start of the study. Patients with a break-through depression displaying a Hamilton Rating Scale for Depression (HAM-D) score of 16 or more for at least two consecutive weeks were included in this study. Symptoms were rated weekly applying the HAM-D scale, the Young mania rating scale and the Global Assessment of Functioning scale (GAF). Sixteen patients received a second mood stabiliser, and 11 patients received paroxetine as an add-on medication to lithium or valproate. All patients receiving paroxetine completed the 6-week study, whereas 6 patients of the group with two mood stabilisers dropped out prematurely. The reasons for drop outs included intolerance, noncompliance, one unrelated medical complication, and in one case the emergence of a mixed state. In the HAM-D, both groups showed significant improvement at all 6 weekly ratings compared to baseline. No significant differences were observed for the Young mania rating scale scores. The author concluded that both treatments show similar efficacy, but that the addition of an antidepressant may be more effective in clinical practice as it is associated with fewer drop-outs and better treatment adherence.

The study appears of clinical interest, but from a methodological standpoint the likelihood of a significant group difference appears impossible due to the small sample size and the add-on design (see the detailed comments below on the study published by Nemeroff et al. 2001). To demonstrate any difference with this design, a huge sample size would be needed. However, this requirement of a huge sample size has been fulfilled in another add-on study, performed by Tohen et al. (2003), which demonstrated an additional significant benefit of adding fluoxetine to olanzapine compared to olanzapine monotherapy. This study is presented in more detail in the section on atypical antipsychotics as supportive evidence for the antidepressant efficacy of olanzapine. However, it is clearly also supportive for the antidepressant efficacy of the antidepressant fluoxetine.

Apart from the more formalistic aspects demanding special trials on antidepressants in the field of acute bipolar depression, based on clinical experience most (European) clinicians have no doubt that antidepressants are effective in the treatment of acute bipolar depression.

Two studies have been performed at the Department of Psychiatry of the Ludwig-Maximilians University, Munich, Germany, to compare the efficacy of antidepressants in unipolar and bipolar depressed patients (Bottlender et al. 2002; Möller et al. 2001). Owing to the fact that apparently the methodological approach of these two publications was misunderstood in some reviews, it is important to explain that these studies were not simply retrospective, naturalistic evaluations based on written patient records, but followed a so-called ex-post prospective design: This means that the data were collected for every patient during his hospital stay in a prospective and standardised way (using standardised assessment procedures!), as part of a huge electronic routine documentation system. Such a database involving thousands of patients can be used to answer different questions at any time. When the discussion about the efficacy or inefficacy of antidepressants came to a climax, it was decided to try to answer this question on the basis of these data. Adequately sized samples of comparable unipolar and bipolar patients were then formed, whereby any bias was avoided. This was the only part of the study that followed an ex-post approach while, as mentioned above, the data collection was prospective and standardised. This type of study is methodologically much more sound and convincing than the typical retrospective evaluation of clinical record data, where the non-standardised data are collected from the written reports and put into the study datasheet. The latter method of retrospective reconstruction of clinical treatment data has a high risk of bias. Furthermore, it relies on data that were primarily not collected using standardised assessment procedures. The ex-post prospective design is not only methodologically superior to such a retrospective design but is also superior to the typical observational/non-blinded treatment study, which mostly focuses on the efficacy of a special drug and is often extremely biased by the hypothesis being investigated and by the investigators' expectations. The ex-post prospective study is widely free of any influence by the hypothesis and investigators' expectations, at least on the level of data assessment, because the raters, i. e. the doctors in charge of each patient, are themselves generally not influenced by the scientific questions and hypotheses which at a later date stimulate the investigators to use thase data in an ex-post sampling.

The fact that the traditional clinical view and conviction that antidepressants are as effective in bipolar as in unipolar depression is not unfounded was demonstrated in two studies which found that the efficacy of antidepressants in inpatients suffering from an acute bipolar depression was equal to that in unipolar depression (Fig. 2). This can be seen as at least indirect proof for the efficacy of antidepressants in acute bipolar depression.

The concerns against the use of antidepressants in bipolar depression are based on the risk of switch to mania and possible induction of rapid cycling (Möller and Grunze 2000). The meta-analysis mentioned above found that the data "do not suggest that switching is a common early complication with antidepressants". The authors continue "It may be prudent to use a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor rather than a tricyclic antidepressant as a first-line treatment" (Gijsman et al. 2004, page 1537).

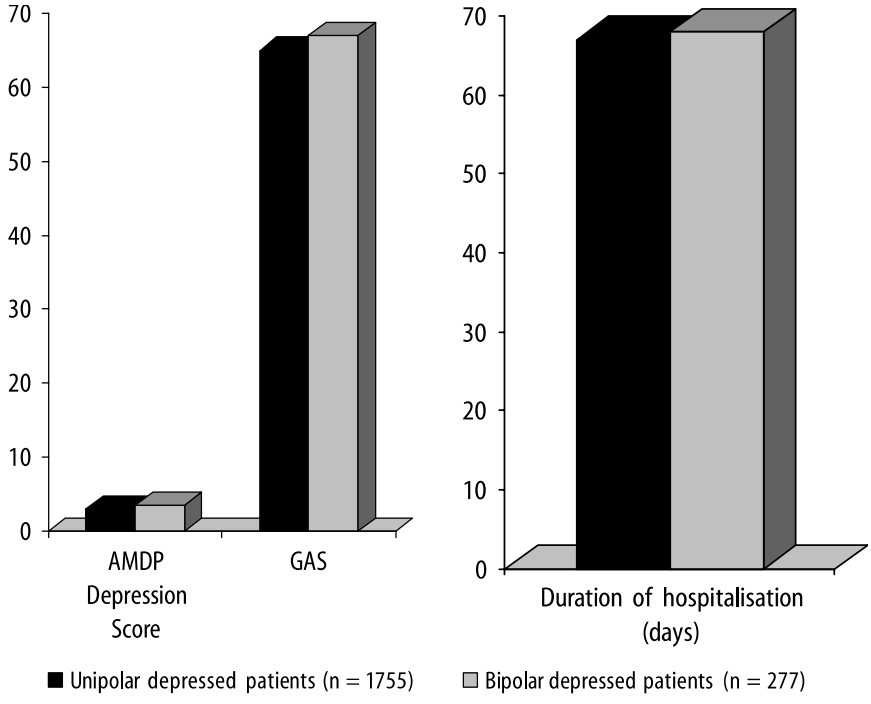

Fig. 2 Efficacy of antidepressants in bipolar compared to unipolar patients (Data taken from Möller et al. 2001)

The evidence for efficacy of mood stabilisers such as lithium or certain anticonvulsants in acute bipolar depression

Having briefly described the evidence for the efficacy of antidepressants in acute bipolar depression, the focus of this chapter will be mood stabilisers.

Lithium

Traditionally, lithium is the mood stabiliser that has been most intensively evaluated with respect to efficacy in acute depression, not only bipolar but also unipolar depression (Adli et al. 1998; Mendels 1976; Souza and Goodwin 1991). To avoid misunderstandings, the following section is only related to the question of acute antidepressive effects of lithium in monotherapy and not to the efficacy of lithium augmentation, which is quite well proven (Bauer et al. 2002).

Lithium has shown a certain antidepressive activity in controlled studies. However, altogether the total number of patients included in these studies was very small. In most studies, no differentiation was made between unipolar and bipolar depression. Several of the controlled studies were not randomised, parallel-group studies, but followed crossover designs with all their known problems and limitations, including hangover and withdrawal phenomena. Because of these methodological problems, crossover designs are not accepted by licensing authorities as proof of efficacy. Most of the randomised, parallel-group studies compared lithium with a standard antidepressant, without a placebo arm. The sample size was extremely small in each of these studies, in general less than twenty patients per treatment group. The conclusion of equal efficacy is completely misleading under these conditions, given the enormous statistical β-error problem. Furthermore, in most of the studies the daily dose of the standard comparator was inadequate, e. g. 100 mg/day or less of a tricyclic antidepressant. Most experts agree that a daily dosage of at least 150 mg of a tricyclic antidepressant is necessary to reach a sufficient treatment response. Without mentioning the other methodological problems from a modern perspective, the essence of these studies with respect to efficacy is weak, a critical position which cannot even be softened by positive sounding meta-analytical approaches or review papers. Lithium seems to have some antidepressive efficacy – for example as shown in the very small placebo-controlled study by Khan et al. (1987) – however, although the power strength of the antidepressive effects compared to antidepressants is widely unclear, the data generally indicate an inferior efficacy. In a head-to-head comparison of lithium with imipramine under controlled treatment conditions, lithium was inferior to imipramine (Fieve et al. 1968). Many patients require lithium treatment for 6–8 weeks before a 'full' antidepressive response becomes evident (Zornberg and Pope Jr 1993).

The APA guidelines (American Psychiatric Association 2002) report the poor evidence in acute bipolar depression quite fairly; however, they omit to discuss the severe methodological problems of crossover designs, which were used in most of these lithium studies. They state the following: "There have been eight placebo-controlled studies of lithium in the treatment of bipolar depression that had five or more subjects. All of these stud-

ies employed crossover designs, and all were completed before 1980 (for a review, see Zornberg and Pope Jr 1993). Among a total of 160 patients, the overall rate of response to lithium, regardless of the degree of improvement or relapse with placebo, was 79 %. However, the "unequivocal" lithium response rate, defined as a good or moderate response to lithium with a subsequent relapse when given placebo, was much lower (36 %). An additional consideration in the use of lithium as an antidepressant is its time to onset (6–8 weeks), which is later than its antimanic effect (Zornberg and Pope Jr 1993)." (American Psychiatric Association 2002, page 26)

Although Bauer and Mitchner stated in their review on mood stabilisers (Bauer and Mitchner 2004) that, compared to the other substances investigated, lithium comes closest to reaching the ideal of a mood stabiliser in the modern sense (Young 2004; Sachs 2005) – it demonstrated the best efficacy in both the acute treatment of mania and bipolar depression as well as in the prophylaxis of bipolar disorder –, the evidence for the efficacy of lithium in acute bipolar depression is quite weak, as described above, and would never be seen by drug authorities such as the FDA or EMEA (CPMP 2001) as being sufficient for licensing.

A recently published multicentre, double-blind, randomised, placebo-controlled study was conducted to assess the efficacy and safety of paroxetine or imipramine as an add-on therapy to ongoing lithium therapy in the treatment of acute bipolar depression (Nemeroff et al. 2001). There is no doubt that this question is of great clinical importance. Outpatients with bipolar disorder who were suffering from a major depressive episode and had been treated with lithium at an effective serum lithium level (see below!) for at least the past 6 weeks were enrolled. All patients (N = 117) fulfilled the DSM-III-R criteria for bipolar disorder and scored ≥ 15 on the 21-item version of the HAM-D. Patients were randomly assigned to receive either paroxetine, imipramine or placebo in addition to their ongoing lithium therapy. Paroxetine patients received 20 mg/day for the first 3 weeks; thereafter, dose increases of 10 mg/day were permitted every 7 days up to a maximum dose of 50 mg/day. Patients receiving imipramine began at a dose of 50 mg/day with a forced titration to 150 mg/day at the rate of 50 mg every 7 days over the first 3 weeks of the study. After this titration period, imipramine dose increases of 50 mg/day were permitted every 7 days up to a maximum dose of 300 mg/day. Dose reduction was permitted once if necessary for adverse events; retitration to the original dose level was allowed if the adverse event remitted. Following the 10-week treatment phase, patients were gradually tapered off all study medications, whereby all patients continued to receive lithium. Serum lithium levels were between 0.5 and 1.2 meq/l (0.4 meq/l for patients intolerant to lithium) for at least 6 weeks before the screening evaluation. Serum lithium concentrations were measured 1 week after initiation of study medication and remained within prior defined levels for all eligible patients. Lithium dose adjustments were not allowed unless serum levels deviated beyond the 0.5–1.2 meq/l range. In the intent-to-treat analyses, mean changes in total score on the HAM-D and CGI severity of illness scale from baseline to endpoint for the paroxetine and imipramine groups were not significantly different than those of the placebo-treated group, i. e. the lithium monotherapy group (Table 2). The mean changes in the HAM-D and the CGI Severity of Illness Scale in the high serum lithium level group were not statistically separated from the paroxetine or imipramine add-on therapy group. However, among the low serum lithium level patients, the add-on therapy with paroxetine or imipramine was superior in terms of mean change from baseline in the total score on the HAM-D

Table 2 Baseline ratings on depression measures for 117 outpatients with bipolar depression randomly assigned to treatment with paroxetine, imipramine or placebo, and changes in scores after 10 weeks (Nemeroff et al. 2001)

	Paroxetine				Imipramine				Placebo			
	Baseline		Change		Baseline		Change		Baseline		Change	
Group and measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total[a]												
Hamilton depression scale	20.38	3.91	−10.2	7.30	20.71	3.90	−10.1	7.26	21.57	3.87	−8.06	7.28
CGI severity of illness scale	4.21	0.69	−1.33	1.38	4.31	0.66	−1.28	1.38	4.33	0.66	−0.91	1.38
Patients with high serum lithium levels[b]												
Hamilton depression scale	20.29	3.78	−9.79	7.11	21.35	3.75	−9.35	7.09	21.95	3.76	−10.4	7.10
CGI severity of illness scale	4.21	0.60	−1.14	1.42	4.35	0.62	−0.94	1.44	4.29	0.60	−1.24	1.42
Patients with low serum lithium levels[c]												
Hamilton depression scale	20.37	4.01	−10.4	7.28	20.11	4.01	−10.7	7.28	21.18	3.99	−5.82	7.32
CGI severity of illness scale	4.21	0.74	−1.47	1.35	4.26	0.74	−1.58	1.35	4.36	0.75	−0.59	1.36

[a] Data set from intent-to-treat population. Paroxetine group, n = 33; imipramine group, n = 36; placebo group, n = 43

[b] Serum lithium level at screening examination > 0.8 meq/l. Paroxetine group, n = 14; imipramine group, n = 17; placebo group, n = 21

[c] Serum lithium level at screening examination ≤ 0.8 meq/l. Paroxetine group, n = 19; imipramine group, n = 19; placebo group, n = 22

and CGI severity of illness scale (Table 2). The responder analysis, using a HAM-D score of ≤7 or CGI Global Improvement score <2 as the criterion, more or less mirrored the results of the mean score changes. Endpoint analysis revealed that no patient treated with paroxetine experienced induction to mania. However, three patients (7.7%) treated with imipramine and one patient (2.3%) treated with lithium alone experienced treatment-emergent mania. Among the three patients treated with imipramine who experienced mania, two were from the low serum lithium level group. The lithium monotherapy patient who developed mania was in the low serum lithium level group. Based on the efficacy data of this study, the authors conclude that patients with bipolar depression who maintain high serum lithium levels may not require additional antidepressant medications. However, patients with low serum lithium levels or those who cannot tolerate high serum lithium levels may benefit from augmentation therapy with either paroxetine or imipramine (Nemeroff et al. 2001).

Without doubt this is a very interesting study which addresses a very important question. However, the methodological limitations of this study, which were presumably caused by limited financial resources and other pragmatic factors, as is often the case in so many other clinical studies which address important clinical questions but which are not funded by drug companies as generously as phase III trials, should not be overseen. Generally speaking, it is always much more difficult to show the efficacy of an add-on therapy than that of a monotherapy. There would possibly have been a similar result if the sequence of lithium and the antidepressants was swapped. Nevertheless, it is a relevant clinical question whether the addition of an antidepressant to ongoing lithium treatment gives an additional therapeutic effect. This approach is based on the hypothesis that lithium already has at least a certain antidepressive effect. The difficulties of proving the efficacy of an add-on therapy in depressive patients, who generally have a high placebo response, increases if very careful methodology, e. g. with respect to sample powering, is not used. In this study the sample size – about 40 patients in each group – was very small, much smaller, for example, than that used in placebo-controlled phase III trials to establish the efficacy of new antidepressants. As is known from meta-analyses of both the FDA and the EMEA files from recent studies on antidepressants, even in these well-powered studies the risk of not showing superiority over placebo is quite high (Khan et al. 2000; Storosum et al. 2001). Drug companies have been aware of this for a long time and tend to perform three phase III studies of this kind to get one positive result. The chance of obtaining a positive result in an add-on therapy approach versus a more or less effective monotherapy condition is principally much lower than the chance in a monotherapy comparison to placebo. The fact that the study by Nemeroff et al. used too small a sample size to investigate the question of an additional efficacy of an add-on treatment with paroxetine or imipramine is demonstrated by their own a priori power calculation. According to this, the study had only 70% power to detect a 5-point difference on the HAM-D between treatment groups. Of course, the assumption of a 5-point difference in the HAM-D score was extremely optimistic in such an add-on design, and would even be too optimistic for a placebo-controlled study on antidepressants. Furthermore, a power of 70% to discriminate between experimental groups is quite low, and would be much lower based on a realistic assumption of the potential difference between the experimental groups. Apart from these principle considerations, the study results themselves also hint at underpowering. Although the differences between the compared groups did not reach the level of statistical significance, the results of the two experimental groups are not on the same numerical level as the lithium monotherapy group: the add-on therapy achieved a more pronounced reduction of about 2 points on average on the HAM-D. A difference of nearly 2 points between the experimental groups and the lithium monotherapy group is close to a level that is generally seen as the average difference between verum and placebo in antidepressant trials (Khan et al. 2000, 2001, 2003; Storosum et al. 2001). Furthermore, a difference of 3 points or more in the HAM-D score is often used as a criterion for inequality of efficacy in trials looking for equivalence. (In this context see for example the results of the lamotrigine study in acute bipolar depression, performed by Calabrese et al. (1999), which is described later in this paper.) It is not astonishing that a difference of 2 points in the HAM-D total score does not reach significance in this trial on a very small sample; but nevertheless, the numerical difference should be discussed. Unfortunately, the authors did not report the time of onset of the antidepressive response, and especially not any differences in the time of onset between the groups. Given the fact that the chosen duration of 10 weeks in this study is quite long and relatively unusual for an efficacy study in acute depression – studies are mostly of 6 weeks duration –, the assumption that a 10-week endpoint might be disadvantageous for the experimental group to demonstrate efficacy seems to be reasonable as spontaneous remission may interfere with the results. Another important confounding factor is the fact that concomitant medications were used in about 80% of the patients. The authors only mention in detail that about 10% of the patients received other mood stabilisers. The other comedication groups (e. g. benzodiazepines!) are not reported. The high proportion of comedication may hide a potential efficacy difference between the experimental group and the lithium monotherapy group. To summarise: this trial does not allow sound conclusions to be drawn. The results are more heuristic than confirmative, as far as the primary question of the study – is an add-on therapy with an antidepressant to ongoing lithium treatment more effective in acute bipolar depression than monotherapy with lithium? – is concerned. In particular the conclusion that in general lithium might be sufficient and that there is

no additional benefit from add-on treatment with antidepressants should not be drawn. Of interest is the additional (ex post?) analysis, showing that the add-on therapy with paroxetine or imipramine is apparently effective in patients with a lithium level in the lower range. It is interesting that apparently the lower level of lithium gives the additional treatment with paroxetine a better chance, showing up as being effective in the statistical sense, even in such a small sample. The question whether the increase of the lithium level in patients with a low lithium concentration would have resulted in the same efficacy as the paroxetine add-on therapy was not investigated in this study. This may have given an indication about the efficacy of lithium in this study, which was not designed per se to prove the efficacy of lithium given the fact that a placebo control for lithium is lacking.

Another very small study (Young et al. 2000), which was already discussed above, aimed to evaluate the addition of an antidepressant versus a second mood stabiliser in inpatients being treated with lithium carbonate or divalproex sodium. Twenty-seven patients were randomly assigned to groups that received double-blind treatment with paroxetine or a second mood stabiliser (lithium carbonate or divalproex sodium) for 6 weeks. Both groups showed significant improvement in depressive symptoms during the 6-week trial. There were more noncompleters in the group being treated with the two mood stabilisers than in the group being treated with a mood stabiliser and paroxetine. The authors conclude that adding an antidepressant to ongoing mood stabiliser treatment is clinically more useful than adding a second mood stabiliser.

Anticonvulsants traditionally used for prophylactic treatment of bipolar disorders – carbamazapine, valproate – a potential treatment for acute bipolar depression?

The database giving hints of antidepressive properties of carbamazapine is much smaller than that for lithium and most of the studies conducted were methodologically not very sound. A meta-analysis of several open and controlled studies, all of which had a small sample size and often made no differentiation between unipolar and bipolar depressive patients, found a response rate of 56 % for depressed patients in the open trials and 44 % for patients in the controlled studies (moderate and good response) (Post et al. 1997). Apparently, the responder rates did not differ between unipolar and bipolar depressive patients, as demonstrated in the studies of Svestka et al. (1991) and Dilsaver et al. (1996), for example.

Early studies by Ballenger and Post (Ballenger and Post 1980) and Post et al. (Post et al. 1986) suggested antidepressant efficacy of carbamazepine. Apart from two schizoaffective patients, the patients described in the article by Ballenger and Post (1980) are also included in the analysis by Post et al. (1986). Therefore, we will concentrate only on the latter of these two studies. The analysis by Post et al. (1986) is based on 35 depressed patients, including 16 patients with bipolar I and 8 patients with bipolar II disorder. Twenty patients (57 %) showed at least mild improvement and 12 of them showed a more substantial improvement as rated by CGI ratings. However, these numbers are difficult to interpret. A separate subanalysis for bipolar and unipolar patients is not available. Although the study has been labelled double blind and placebo controlled, this is not true according to today's methodological standards. It is not a parallel-group study comparing one group with carbamazepine and one group with placebo. All patients had a placebo run-in phase of variable length, and it was unknown to nurses and patients when active treatment of carbamazepine started and was finished. The length of both the placebo run-in and the active treatment phase were variable; the mean duration of the placebo run-in phase was 55 ± 41 days. No information is supplied about the average duration of carbamazepine treatment, but a significant improvement is reported at weeks 3 and 4. Thus, taken together, this study may be supportive for an antidepressant effect of carbamazepine, but it definitely does not supply convincing evidence due to its severe methodological limitations.

The database for valproate is similarly weak. The open study by Winsberg et al. (2001) in 19 bipolar II depressive patients reported that 63 % responded in terms of a 50 % reduction in HAM-D total score. In an open study, Calabrese and Delucchi (1990) found a marked improvement in 57 % of the patients. In an open study with the largest sample of 103 patients, however, a moderate improvement was only found in 22 % of the patients (Lambert 1984).

In a recently presented, 8-week study (Sachs et al. 2002), valproate was evaluated in a randomised, placebo-controlled design. In the intent-to-treat analysis of 43 subjects, 9 of 21 subjects (43 %) treated with divalproex sodium met criteria for recovery at the final assessment compared to 6 of 22 subjects (27 %) treated with placebo ($p < 0.4$). The divalproex sodium-treated subjects demonstrated improvements in the mean changes from baseline in HAM-D total scores over the course of the trial that were numerically superior to placebo at every time point, and approached statistical significance on weeks 2 and 5. The divalproex sodium-treated subjects also had improvements in the HAM-D depressed mood item that were numerically superior to placebo at every follow-up assessment, with statistical significance (weeks 2, 4, and 5) or trends toward significance (week 3) reached at several time points. Due to the small sample size ($n = 43$), in the primary outcome measure, the HAM-D total score, the difference between the groups failed to reach the level of significance.

Lamotrigine

With respect to the current methodological standards in the field of the evaluation of antidepressive efficacy of anticonvulsants used in the field of bipolar disorders, the placebo-controlled study on lamotrigine, involving 195 patients, seems paradigmatic (Calabrese et al. 1999). The study was based on positive findings of some open clinical studies and observations giving a hint to antidepressive properties of lamotrigine (Hahn et al. 2004). In this study, in which 200 mg lamotrigine per day was compared to 50 mg lamotrigine per day and to placebo, lamotrigine 200 mg/day was seen to be effective in acute bipolar depression. Special aspects and limitations of the results of this study will be discussed below. The positive findings for lamotrigine were received with great enthusiasm, which is reflected among others by the fact that this study was apparently judged as giving enough evidence to allow recommendation of lamotrigine as first line treatment, besides lithium, of acute bipolar depression in the revised APA guideline on the treatment of bipolar disorder (American Psychiatric Association 2002). This unusual success in the clinical and scientific community might be explained by the fact that due to its high methodological standard this study can still be seen as a landmark in the evaluation of 'mood stabilisers' in the treatment of acute bipolar depression. In order to evaluate the results of this study more carefully it seems necessary to describe and analyse this and other lamotrigine studies in greater detail with respect to methodology and efficacy results.

This multicentre, double-blind, fixed-dosed, control-group study compared a 7-week treatment with lamotrigine (50 or 200 mg/day) or placebo (Calabrese et al. 1999). A total of 195 outpatients with bipolar I disorder according to DSM-IV criteria who were experiencing a major depressive episode with a score of at least 18 on the HAM-D-17 scale were recruited (66 in the lamotrigine 50 mg/day group, 63 in the lamotrigine 200 mg/day group and 66 in the placebo group). The depressive episode had to be present for at least two weeks but not longer than a year. Patients had to have had at least two previous mood episodes during the past ten years, at least one of which had to have been a manic or mixed episode. The usual additional inclusion and exclusion criteria were applied. Patients who were unable to tolerate the target dose of 200 mg/day were allowed a single dose decrease at any time after day 31, and those who were unable to tolerate the lower dose were withdrawn from the study.

A total of 192 patients were included in the statistical analyses (64 from the lamotrigine 50 mg/day group, 63 from the lamotrigine 200 mg/day group and 65 from the placebo group). The mean change from baseline in the HAM-D-17 score was defined a priori as the primary efficacy analysis. Several secondary measures of efficacy were included such as the mean change from baseline of the Montgomery-Asberg Depression Rating Scale (MADRS) total score, the change in score of the HAM-D Item 1 and the CGI. The average baseline HAM-D-17 score, approximately 24, was consistent with the characterisation of the patients as suffering from moderately severe depression and was comparable between treatment groups.

The intent-to-treat analyses showed that patients treated with lamotrigine had a greater decrease in HAM-D-17 scores than those treated with placebo. Although the difference between groups was not statistically significant, there was a trend towards significance in favour of the lamotrigine 200 mg/day group. The mean change from baseline in the LOCF analysis amounted in the placebo group to –7.8, in the lamotrigine 50 mg group to –9.3 and in the lamotrigine 200 mg group to –10.5. The numerical differences compared to placebo did not reach statistical significance.

In contrast to these non-significant results, lamotrigine differed significantly from placebo, particularly at the 200 mg dose, on a number of secondary efficacy parameters. Patients treated with lamotrigine had a greater decrease in the MADRS mean score than those treated with placebo. Mean change of the MADRS score (LOCF analysis) in the placebo group was –7.8, in the 50 mg lamotrigine group –11.2 and in the 200 mg lamotrigine group –13.3. This was significant for the 200 mg lamotrigine group ($p < 0.05$). Patients treated with lamotrigine also had a greater decrease in the CGI-Severity mean score than those treated with placebo. The difference between the lamotrigine 200 mg and placebo group was statistically significant ($p < 0.05$). Also the difference in the CGI-Improvement score between the 200 mg lamotrigine group and the placebo group was statistically significant ($p < 0.05$). As to the HAM-D Item 1 mean score changes (LOCF analysis), there was a statistically significant difference between lamotrigine and placebo at the end of the study for the 200 mg lamotrigine group ($p < 0.05$), and for the 50 mg group ($p < 0.05$). The observed case analyses showed more significant results than the LOCF analysis, among others a significant difference in the primary endpoint.

The HAM-D responder analysis did not show a statistically significant difference in favour of lamotrigine, although there were numerical differences. The 50 % reduction of the HAM-D-17 score responders amounted to 37 % in the placebo group, 35 % in the lamotrigine 50 mg group and to 51 % in the lamotrigine 200 mg group. The responder analysis in the MADRS scale showed statistically significant differences: 29 % in the placebo group, 48 % in the lamotrigine 50 mg group and 54 % in the lamotrigine 200 mg group. The same is true also for the CGI-I responders (very much improved/much improved): 26 % vs. 41 % vs. 51 % ($p < 0.05$).

As already mentioned these results were seen by many clinicians as demonstrating or even proving the efficacy of lamotrigine in acute bipolar depression. However, judged from a more formalistic, strictly statistical methodological standpoint, which is the general position of licensing authorities such as the US-American (FDA) or the European drug authority (EMEA)

(CPMP 2001), the results of this study have severe limitations. The most crucial point is that in the ITT analysis lamotrigene failed to show a significant difference in the primary efficacy criterion, the change in the HAM-D score. It is also remarkable that no dose-efficacy relationship was observed between 200 mg/d lamotrigine and the very low dose of 50 mg/d. Given the a priori definition of outcome criteria, the study thus failed to be confirmative. However, there were some statistically significant differences in the secondary outcome efficacy criteria, which could lead to the general results of the study being interpreted as supportive on a certain level. Nevertheless it has to be questioned why, based on the results of this study, lamotrigine, beside lithium, was implemented in the revised APA guidelines (American Psychiatric Association 2002) as well as in the consensus paper by Sachs et al. (2000b) as the first-rank treatment in acute bipolar depression.

Although the study was not confirmative, it gave hope in the expected direction. A second, similarly designed study was performed to evaluate the efficacy of lamotrigine in the treatment of acute bipolar depression. This was a multicenter, double-blind, placebo-controlled flexible dose (100–400 mg/d lamotrigine), 10-week study on the treatment of major depressive disorder in patients with bipolar disorder. In this study not only patients with bipolar I but also with bipolar II disorder were enrolled (100 in each arm). The primary efficacy criterion was the HAM-D-17 score change from baseline. The results of this study were presented during the APA meeting 2001 by Ascher (2001), however, hitherto they have not been fully published. As communicated in a short notice by Bowden (2002) in his review on lamotrigine in the treatment of bipolar disorder, the study did not indicate a significant difference between lamotrigine and placebo. The proportion of patients responding under placebo was higher in this trial. The secondary analyses of subgroups presented evidence of a benefit to the bipolar I subjects.

There is no doubt that this is a negative study that does not give any hint about efficacy in any depression parameter. However, for a fair and balanced view it has to be considered that it is well known in the field of studies of modern antidepressants that apparently quite a high proportion of these studies fail to prove efficacy of the experimental drug in comparison to placebo (Khan et al. 2000, 2001, 2002a, 2002b, 2003; Khan and Brown 2001; Storosum et al. 2001). Based on all dossiers delivered to the FDA or EMEA the ratio of one positive study per three phase III studies is more or less the average. Thus one negative study and one supportive study does not mean that there is no chance to prove efficacy of lamotrigine in treating acute bipolar disorder. Unfortunately, as far as we are aware at the moment no other lamotrigine studies in acute bipolar depression are either completed or even ongoing. Therefore a final answer cannot yet be obtained.

There are, however, study results from trials on unipolar depression which can at least contribute to the global picture of efficacy of lamotrigine in depression and provide further hints as to whether lamotrigine might have antidepressive properties. Especially if it is assumed that the antidepressant effect of psychoactive drugs is syndromatic and not specifically related to certain disorders (see above), the results of studies on the acute treatment of unipolar depression also have consequences for the field of acute bipolar depression.

In a large, multicenter, double-blind, randomised, placebo-controlled, fixed-dose study on 453 unipolar depressive patients, lamotrigine 200 mg/day (152 patients) was compared to placebo (150 patients) and desimipramine 200 mg/day (151 patients). The treatment duration was eight weeks, which included a dose escalation period of five weeks for lamotrigine and four weeks for desimipramine. The primary efficacy measure was the HAM-D-17 score change from baseline; the secondary measures were the same as in the studies on acute bipolar depression. Patients with moderate to severe unipolar depression were included applying the usual additional inclusion and exclusion criteria. The results of this study were also presented during the APA meeting 2001 by Ascher (2001), but apparently a full report of the study has not yet been published. In his review on lamotrigine in the treatment of bipolar disorder, Bowden (2002) wrote that significant improvements were found on the global impression of severity measure at some time points with both lamotrigine and desimipramine compared to placebo. However, the primary outcome measures did not indicate superiority for either lamotrigine or desimipramine in the trial. The high risk not only to be unable to demonstrate efficacy of the experimental drug versus placebo in depression but also of not being able to demonstrate efficacy of the standard antidepressant versus placebo, the risk of a so-called "failed study", is well known from the dossiers of modern antidepressant drug trials at the FDA or EMEA (Khan et al. 2000, 2001, 2002a, 2002b, Khan and Brown 2001; Storosum et al. 2001). Two other large studies comparing lamotrigine with placebo in unipolar depression have been performed. The results have not been reported so far.

A double-blind study on a very small sample investigated the efficacy of paroxetine combined with lamotrigine versus paroxetine monotherapy in depressed patients (Normann et al. 2002), with the vast majority of patients suffering from unipolar depression. Forty patients with a depressive episode (DSM-IV criteria) requiring psychiatric intervention received lamotrigine or placebo using a fixed dose escalation scheme with a target dose of 200 mg/day for 9 weeks. Additionally, all patients were treated with paroxetine. The HAM-D and Clinical Global Impressions scale (CGI) ratings were used to monitor therapeutic efficacy. Adjunctive treatment with lamotrigine did not result in a significant difference in HAM-D total score at the endpoint of the study when compared with paroxetine alone. There is no doubt that this study was unable to answer the main question for methodological reasons, especially con-

cerning sample size, as was discussed above in the context of the study by Nemeroff et al. (2001).

Another small (n = 31), placebo-controlled, cross-over study showed that lamotrigine was superior to both placebo and gabapentin in patients entering in with depressed episode, whereas gabapentin did not differ from placebo (Frye et al. 2000). The methodological limitations of cross-over studies have already been discussed above.

All together the results of the lamotrigine studies in acute bipolar depression, as well as the additional evidence from the lamotrigine studies on acute unipolar depression, do not support the view that lamotrigine should be the treatment of first choice in acute bipolar depression. Theoretically, it is an interesting paradox that lamotrigine is effective in preventing depressive relapses of bipolar disorders (Severus et al. 2005) but has no consistently proven efficacy in treating acute bipolar or unipolar depression.

Second generation antipsychotics

Beside the indication schizophrenia, second generation antipsychotics are being increasingly evaluated in the field of bipolar disorders. The main targets are the acute manic episode and the maintenance therapy of bipolar disorders (Grunze and Möller 2003). Recently, also the indication acute bipolar depression has become a focus of interest in the clinical development of second generation antipsychotics. This recent interest in bipolar depression was induced by the special pharmacological mechanisms of second generation antipsychotics, which seem to indicate that they have antidepressive properties (Möller 2005b; Roth et al. 2003). This expectation is supported by an increasing body of clinical evidence showing that second generation antipsychotics are efficacious in reducing depressive symptoms of patients in an acute schizophrenic episode; furthermore, four studies also showed efficacy of second generation antipsychotics in major depression, especially treatment-refractory depression (Möller 2005a).

The general aim is to develop second generation antipsychotics as mood stabilisers in the modern sense, i. e. as drugs which have the capacity to prevent and to control manic or depressive episodes in bipolar disorders without inducing the symptomatology of the opposite pole. Of the traditional substances applied in this field – lithium and anticonvulsants –, only lithium seems to fulfil this ideal to a certain degree (Bauer and Mitchner 2004). However, as discussed above, the antidepressive effect of lithium is only based on methodologically weak evidence and does not appear to be very strong.

Two recent studies which applied high methodological standards appear to support the hypothesis that second generation antipsychotics have an antidepressive effect in acute bipolar depression. In the first, fully published combined analysis of two identically designed studies, a total of 833 adults with acute bipolar I depression with an MADRS score of at least 20 were investigated in a double-blind, 8-week, randomised controlled design (Tohen et al. 2003). Patients were randomly assigned to receive placebo (n = 377), olanzapine, 5 to 20 mg/day (n = 370), or olanzapine-fluoxetine combination, 6 and 25, 6 and 50, or 12 and 50 mg/day (n = 86). A difference in the MADRS total scores was defined a priori as the main efficacy criterion. The mean modal drug dose was 9.7 mg/d for the olanzapine monotherapy group, and 7.4 mg/d for olanzapine and 39.3 mg/d for fluoxetine for the combination group. The percentage of patients who used benzodiazepines at least once during the study was not statistically significantly different between the groups (placebo group, 43.5 %; olanzapine group, 43 %; olanzapine-fluoxetine group, 36 %; overall $p = 0.44$). Efficacy results showed mean ± SD baseline MADRS scores ranging from 30.8 ± 6.1 to 32.6 ± 6.2. There were significant main effects for treatment ($p < 0.001$) and for visit ($p < 0.001$), with no significant treatment × visit interaction ($p = 0.43$). Between-group comparisons for visit-wise MADRS mean change were as follows: Starting as early as week 1 and continuing throughout the study, the olanzapine and olanzapine-fluoxetine groups demonstrated significantly greater mean improvements in MADRS total scores than those receiving placebo. Starting at week 4 and continuing to week 8, the olanzapine-fluoxetine group also demonstrated significantly greater mean improvement in MADRS total scores than the olanzapine monotherapy group. The therapeutic effect sizes for olanzapine and olanzapine-fluoxetine were 0.32 and 0.68, respectively. The response rate for the olanzapine group was 39 % (137/351), which was significantly higher than the rate for the placebo group of 30.4 % (108/355; $p = 0.02$). The response rate for the olanzapine-fluoxetine group was 56.1 % (46/82), which was significantly higher than that for the placebo ($p < 0.001$) and olanzapine ($p = 0.006$) groups. Median times to response for the placebo, olanzapine and olanzapine-fluoxetine groups were 59, 55 and 21 days, respectively. Time to response was significantly shorter for the olanzapine group compared with the placebo group ($p = 0.01$), and shorter still for the olanzapine-fluoxetine group compared with the placebo ($p < 0.001$) and the olanzapine ($p = 0.005$) groups. The remission rate for the olanzapine group was 32.8 % (115/351), which was significantly higher than the rate for the placebo group of 24.5 % (87/355; $p = 0.02$). The remission rate for the olanzapine-fluoxetine group was 48.8 % (40/82), which was significantly higher than that for the placebo ($p < 0.001$) and olanzapine ($p = 0.007$) groups. Median estimated times to remission for the placebo, olanzapine and combination groups were 59, 57 and 42 days, respectively. Time to remission was significantly shorter for the olanzapine group compared with the placebo group (Tohen et al. 2003).

Of great interest are the analyses of individual MADRS items. The olanzapine and olanzapine-fluoxetine groups showed statistically significant improve-

ments on inner tension, reduced sleep and reduced appetite compared with the placebo group. In addition, the olanzapine-fluoxetine group showed statistically significant improvement on core mood items, including apparent sadness, reported sadness, lassitude, inability to feel, and pessimistic thoughts, compared with the olanzapine and placebo groups. These results could be interpreted as a hint that olanzapine alone might not be able to influence the core items of depression.

These results demonstrate antidepressive efficacy of olanzapine in acute bipolar depression. However, the efficacy of the combination of olanzapine and fluoxetine is greatly superior, indicating that the antidepressive efficacy of olanzapine alone is possibly not the strongest and can be surpassed by combining it with an antidepressant. In this context it is interesting that the item-related analysis of efficacy suggests that olanzapine alone merely has effects on core depression items. As there was neither a fluoxetine monotherapy arm nor a monotherapy arm with another antidepressant, the question remains whether the antidepressive efficacy of olanzapine alone in this condition is on the level of antidepressants and therefore requires further investigation.

In an 8-week, randomised, double-blind clinical study two fixed doses of quetiapine – 300 mg/d or 600 mg/d – were compared to placebo in 542 patients with bipolar I and II disorders. The complete study results have not yet been published as a full paper; however, the main results were presented by Calabrese et al. as an abstract at the APA Congress 2004 (Calabrese et al. 2004a). In addition, the main results were sent to several experts in the form of a press release by the company Astra Zeneca. Patients taking quetiapine achieved a significantly greater improvement ($p < 0.001$) in mean MADRS and HAM-D scores versus placebo at every time point starting at week one and through to week 8. Significantly more patients taking quetiapine ($p < 0.001$) were considered to be responders (> 50 % decrease from baseline MADRS score) from week 2 through to the end of the study. After 8 weeks, significantly more patients taking quetiapine achieved remission from their depressive symptoms compared to the placebo group (53 % vs. 28 %, respectively, $p < 0.001$) as evaluated on the MADRS scale. Interestingly, statistically significant antidepressant efficacy could only be demonstrated for the total group of patients and the bipolar I subgroup, but not for bipolar II patients. However, this difference is likely due to methodological shortcomings (smaller sample size for bipolar II and higher placebo response), and may not reflect biological differences.

All together this study shows an antidepressive effect of a new antipsychotic in acute bipolar depression. The effect size in this study was significantly larger than in the olanzapine study described above. However, caution is advised when comparing the results of two different studies in terms of 'effect size'. As this was a study without an antidepressant control arm, the question whether the antidepressive efficacy of quetiapine is on a comparable level to that of antidepressants still remains unanswered and requires further investigation. Further details have to be reviewed when the study has been fully published.

In this context it should be carefully considered that also other psychopharmaceuticals, such as the benzodiazepines, especially alprazolam, have demonstrated a certain antidepressive efficacy, in this case in unipolar depression, although the effect was not on the same level as that of the antidepressant, at least not in severe depression (Laakman et al. 1986; Möller 1992; Montgomery and Lecrubier 1999).

Regulatory requirements for a claim of 'acute bipolar depression'

As clinical thinking is often far away from regulatory criteria, and especially as in the field of bipolar disorders there is a huge gap between guideline recommendations and drug licences, the essence of the regulatory requirements is presented below.

The evaluation of a drug intended for use in the acute treatment of bipolar depression needs to be performed in parallel group, randomised double-blind comparisons against placebo. However, from the European perspective (CPMP 2001, 2002) three-arm studies including the new product, placebo and an established active comparator are preferred. Patients with both bipolar I and bipolar II disorder might be included; however, the possibility of a subgroup analysis should then be described and justified in the study protocol. The study period for investigations of treatment for acute bipolar depression should be in line with the studies in unipolar depression, which in general are of 6 to 8 weeks' duration. Improvement should be shown as a significant difference on the pivotal scales between baseline and post-treatment score in symptomatology, but should also be expressed as the proportion of responders (e. g. proportion of patients with 50 % improvement). The sample size should be calculated on the assumptions underlying the primary analysis; however, it may be useful to take the clinical relevance (responders) into consideration as well. The statistical analysis should include various analyses, among others intent-to-treat (ITT) and per protocol. However, the ITT analysis should be the primary analysis. Due to the complicated course of bipolar disorder, the handling of drop-outs and missing data should be prospectively planned in the trial protocol (Broich 2003).

From the European perspective of the CPMP (CPMP 2001, 2002) and the respective ECNP consensus meeting (Montgomery 2001), before licensing ideally studies in both unipolar and bipolar depression should be performed. Efficacy shown in both conditions would strengthen the result in bipolar alone, whereas a negative result in unipolar depression will have consequences for the Summary of Product Characteristics (SPC). Results from studies with antidepressants in unipolar depression may be partly extrapolated to bipo-

lar depression. However, results from studies in bipolar depression (e. g. treatment with mood stabilisers or atypical neuroleptics) cannot be extrapolated to unipolar depression. At least two unequivocal positive placebo-controlled studies in bipolar depression or one in unipolar and one in bipolar depression may be sufficient to establish efficacy in bipolar depression.

When monotherapy has already been established as effective and safe, it may be useful to examine whether the combination of the new medicinal product with an established mood stabiliser in placebo-controlled, add-on designs might provide additional therapeutic advantages. However, the demonstration of an advantage of the combination treatment in comparison with the established mood stabiliser alone allows no extrapolation that the new agent itself is effective in monotherapy.

Among the usual adverse drug reactions the risk and rate of switching to hypomania or mania is considered as a highly important issue with respect to safety in patients with bipolar disorder. Switching criteria need to be predefined and its incidence needs to be established in relation to the active comparator as well as placebo (Broich 2003).

Conclusions

Despite the fact that bipolar depression is the predominant mood state for the vast majority of patients with bipolar disorder, the focus of research and randomised clinical trials in the management of bipolar disorder has mainly been on mania. Although clinical treatment algorithms are now available that take into account the particular characteristics of bipolar depression, data from randomised clinical trials fulfilling the requirements for regulatory approval of the indication bipolar depression are limited.

The antidepressive efficacy of traditional mood stabilisers like lithium or several anticonvulsants is not well proven, at least not following the methodological standards that are commonly used to establish the efficacy of antidepressants. Although there are some hints for an antidepressive efficacy of mood stabilisers like lithium, and for lamotrigine, the question remains open whether the proof of its antidepressive efficacy is sufficient and whether the supposed antidepressive efficacy is comparable to that of antidepressants. At least some data show a lower efficacy of lithium compared to antidepressants or to co-medication of lithium with antidepressants. This question in particular requires further evaluation before a final conclusion can be drawn whether antidepressants should be replaced by lithium or other mood stabilisers generally, or under certain conditions, in the treatment of acute bipolar depressions. Of course, the tolerability of traditional and modern antidepressants compared to the recommended mood stabilisers also has to be taken into consideration. Some of the mood stabilisers have an unfavourable side effect profile, at least compared to modern antidepressants.

Of course, lithium can still play a certain role in the indication 'acute bipolar depression', especially in mild and possibly in moderate depression. The evidence for valproate and carbamazepine is extremely weak. The position of lamotrigine is ambiguous due to the inconsistent findings in the pivotal studies on bipolar depression and, if the results of the pivotal studies in unipolar depression are also taken into account, the data do not appear very convincing, in contrast to the excellent data on the prevention of depressive episodes in bipolar disorder. The efficacy data of the second generation antipsychotics olanzapine and quetiapine seem promising. However, they require further evaluation, including studies versus modern antidepressants.

Thus in the current situation, antidepressants still appear indicated to obtain a good antidepressive response, at least in moderate and severe acute bipolar depression. In acute bipolar depression the main goal should be to obtain an optimal antidepressive response, as is the first aim in the treatment of unipolar depression. In particular the view, which is increasingly respected in the field of treatment of unipolar depression, that not only response but also remission of the depressive symptoms should be achieved (Hirschfeld et al. 2002; Keller 2003), has to be transferred to the field of treatment of acute bipolar depression. Of course, the risk of switch has to be critically considered but with the use of modern antidepressants like the SSRIs and with the protection of mood stabilisers this risk can be controlled quite well (Bottlender et al. 2001; Gijsman et al. 2004). Thus patients suffering from acute bipolar depression should not be left without this powerful treatment of their depressive symptoms (Gijsman et al. 2004; Möller and Grunze 2000).

This conclusion matches well the conclusions drawn by Gijsman et al. (2004) based on their meta-analysis: "We will compare our current conclusions with the recent APA Practice Guideline for the Treatment of Patients with Bipolar Disorder (American Psychiatric Association 2002) on two key points. First, there is no strong reason to avoid antidepressants for patients with bipolar depression. This is at odds with the recommendation to use lithium or lamotrigine as a first-line of treatment for bipolar depression. For patients already taking a mood stabilizer, we advise adding an antidepressant as a first-line treatment. For patients not taking a mood stabilizer but with a history of mania, the current consensus is to use antidepressants in combination with an antimanic agent or a mood stabilizer (Goodwin 2003)." (Gijsman et al. 2004, page 1545). In the final part of their paper the authors are very precise in describing the risk of restricting antidepressants in the field of acute treatment of bipolar depression: "On the basis of current evidence, we believe that it is overcautious and potentially not in the best interest of patients to discourage the use of antidepressants for bipolar depression. We appreciate that the existing APA guidelines do recommend the use of specific antidepressants for severe depression. However, in practice, we have seen cases

in which patients have not been treated with antidepressants and have been left chronically and significantly depressed for very long periods of time. This is almost certainly one consequence of an emphasis on the first-line use of mood stabilisers such as lithium and valproate for bipolar depression, despite the inadequate evidence that they actually work." (Gijsman et al. 2004, page 1545).

As to the use of antidepressants in bipolar depression, the bipolar depression guidelines of the World Federation of Societies of Biological Psychiatry (Grunze et al. 2002) and those of the British Association of Psychopharmacology (Goodwin 2003), as well as the North American Expert Consensus on Medication Treatment of Bipolar Disorder (Sachs et al. 2000b) are open to accepting the necessity of this medication, especially of second generation antidepressants, not only in severe but also in mild and moderate depression. Interestingly, in the American consensus paper, which was based on the statements of 65 American experts, the recommendation for the duration of antidepressant treatment is quite unrestrictive, which may be based on the respective results from the Stanley network (Altshuler et al. 2003). For more severe depressions, most experts recommended continuing antidepressant treatment for 2 to 6 months beyond the point of remission before tapering, although about 25 % of the experts would continue the antidepressant indefinitely. A slightly shorter period is recommended for patients with a less severe episode (Sachs et al. 2000b). These positive statements are unfortunately counterbalanced by the paper of a small, international consensus group (7 experts) (Calabrese et al. 2004b) in which the place of antidepressants in the indication acute bipolar disorder is again seen very restrictively and where the positive evidence for mood stabilisers in the classical sense (lithium, anticonvulsants) seems to be exaggerated.

Beside these ongoing controversies regarding the use of antidepressants in the treatment of acute bipolar depression, another eminent problem is that most of the drugs suggested in the most recent guidelines for the treatment of acute bipolar depression are not licensed for this indication, and several of them will apparently never obtain a licence. This gap between guideline recommendations and the licensing situation brings the treating physician into the unpleasant situation of off-label use with all its negative legal and insurance-related consequences. Only the antidepressants are in a better situation, given the fact that at least the older antidepressants have an unrestricted licence for depression (as a syndrome), not restricted to aetiological or classificatory subtypes, and also that the modern antidepressants have the general indication 'major depressive episode'.

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