Eur Arch Psychiatry Clin Neurosci (2000) 250: 57–68 © Steinkopff Verlag 2000

ORIGINAL PAPER

H.-J. Möller · H. Grunze

Have some guidelines for the treatment of acute bipolar depression gone too far in the restriction of antidepressants?

Received: 3 January 2000 / Accepted: 2 February 2000

Abstract This paper gives a critical review of recommendations concerning the drug treatment of acute bipolar depression. The suggestions of different guidelines and consensus papers, especially in US-American and Canadian psychiatry, have a strong tendency against antidepressants in bipolar depression; they prefer mono-therapy with mood stabilizers and, in the case of co-medication with mood stabilizers and antidepressants in severe depression, to withdraw the antidepressant as early as possible. The intention of this restrictive use is to avoid the risk of mania and the risk of rapid cycling induced by antidepressants. However, apparently the risk of suicidal acts, which is as prominent in bipolar depression as in unipolar depression, has been totally neglected. Furthermore, the fact that none of the mood stabilizers have proven their antidepressive efficacy leads not only to the risk of depression-related suicidal behavior but also to the risk of chronicity of depressive symptoms due to undertreatment. Altogether the view expressed in some guidelines and consensus papers appears not well balanced. Furthermore, the fact that apparently the selective serotonin re-uptake inhibitors and possibly some other modern antidepressants have only a low risk of inducing a switch to mania should stimulate a rewriting of the guidelines on drug treatment in acute bipolar depression in a less restrictive way concerning the use of antidepressants.

Key words Bipolar depression · Tricyclic antidepressants · Selective serotonin re-uptake inhibitors · Drug treatment of acute bipolar depression

Prof. H.-J. Möller (✉) · H. Grunze
Psychiatrische Klinik
der Ludwig-Maximilian-Universität
Nussbaumstr. 7
D–80336 Munich
Germany

Introduction

In German psychiatry and in psychiatry in some other countries, antidepressants have a long tradition of being the drug of first choice in the treatment of acute bipolar depression. This is a tradition which still has a strong impact on treatment decisions in current routine treatment (Kasper et al. 1999; Walden et al. 1999). However, other countries, especially the United States, are increasingly restrictive concerning the use of antidepressants in this indication (Hirschfeld et al. 1994; Sachs 1996).

Especially in US-American and Canadian psychiatry, there is a strong tendency to avoid antidepressants in bipolar depression and to prefer a monotherapy with mood stabilizers in less severe depression, and, in the case of co-medication with mood stabilizers and antidepressants in severe depressions, to withdraw the antidepressants as early as possible. This tendency has been expressed 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 reflects this tendency (Goodwin and Nolen 1997).

The recommendations published in the different papers and guidelines are not identical but, with certain differences, they follow a similar general direction: avoid the use of antidepressants in mild, possibly also in moderate, depression, and in general only use antidepressants if they are "clinically necessary", whatever the latter term, which is not defined or operationalized in any way, means.

Possibly the risk of mania and risk of rapid cycling induced by antidepressants has been overestimated in comparison to the risk of suicidal acts and chronicity. Of course, it is difficult to make the right decision between Scylla and Charybdis. Nevertheless, suicidality seems to be the more critical outcome. Coming from this position, the questions have to be posed: Have we lost a well-balanced view? Have we gone too far in the restriction of antidepressants?

Apparently, the restriction of antidepressants in the guidelines and experts' recommendations is based on the following arguments, which are either clearly expressed in the respective publications or are more or less latent in the argumentation:

- The risk of switching into mania/rapid cycling induced by antidepressants is an important clinical phenomenon in bipolar depression.
- The risk of suicidality, suicide attempts and suicide in bipolar depressive patients is of minor clinical relevance.
- The antidepressive efficacy of antidepressants in bipolar depression is insufficiently proven.
- The antidepressive efficacy of mood stabilizers in bipolar depression is sufficiently proven.
- Conclusion: avoid antidepressants, except in severe cases; give priority to mood stabilizers for the treatment of bipolar depression.

The aim of the following paper is to discuss these arguments, which are apparently the principal basis for the guidelines and recommendations mentioned above, in the light of the existing empirical evidence.

Argument 1: The risk of switching into mania/rapid cycling is an important phenomenon in bipolar depression

The risk rate of switching into mania shows a broad spectrum in the literature, from about 10 to 70% (Akiskal et al. 1977; Altshuler et al. 1995; Bunney Jr 1978; Prien et al. 1984; Quitkin et al. 1981; Wehr and Goodwin 1979a). The early studies, which are mostly retrospective and related to tricyclic antidepressants (TCA), seem to overestimate the switch risk, possibly due to selected samples (Grunze et al. 1999). A meta-analysis of 80 publications covering a total of about 4,000 patients with bipolar depression or unipolar depression, not showing a bipolar history or feature at the time of the study, found a switch rate of 9.6% for tricyclic antidepressants and for MAO inhibitors (Bunney Jr 1978). In his meta-analysis on all available data from clinical trials comparing SSRIs, TCA and placebo, Peet (1994) differentiated between unipolar and bipolar depressive patients; while the switch rate of the unipolar patients under tricyclic antidepressants amounted to less than 1%, the switch rate among bipolar patients was about 10-fold higher (11.2%). Peet also differentiated in his analysis between different treatment groups of bipolar depressive patients. While the risk rate of switching into mania under TCAs amounted to 11.2%, the respective risk rate under SSRIs was 3.7%, and under placebo 4.2%.

In a study comparing fluoxetine, imipramine and placebo (Cohn et al. 1989) in a smaller sample of acute bipolar depressive patients, the switch rate under imipramine was 9.5%, under placebo 7.7%, and under fluoxetine 0%. Other modern antidepressants like the selective and reversible MAO-A inhibitor moclobemide (Baumhackl et al. 1989) or the dopamine angonist buproprione (Sachs et al. 1994) also showed a more favorable switch rate risk compared to tricyclic antidepressants.

In some of the studies mentioned above, the concomitant treatment with a mood stabilizer was not considered, which might lead to an underestimation of the switch rate under antidepressants. Thus, the study by Himmelhoch et al. (1991), in which concomitant mood stabilizers were not allowed, is of interest: this group found a switch rate of 38% for anergic bipolar I patients treated with antidepressants (imipramine or tranylcypromine) over a 16-week period.

In a naturalistic study on 29 bipolar I patients, Boerlin et al. (1998) found that switches to hypomania occurred in 28% of the overall number of episodes. Depressive episodes treated with tricyclics or MAO inhibitors showed a higher risk for switching than those treated with fluoxetine. Based on a within-subject analysis between patients who received mood stabilizers and those who received mood stabilizers plus an antidepressant, Boerlin concluded that mood stabilizers may reduce the risk for switching. Patients who were treated with an antidepressant and a mood stabilizer as a co-medication had no higher a risk of switching into mania than patients who were treated with a mood stabilizer alone. The protective function of mood stabilizers, in this case lithium, can also be derived from long-term studies on bipolar depression in which patients were treated with imipramine and lithium (Prien et al. 1984; Quitkin et al. 1981).

Rouillon et al. (1992) provided an overview of 15 long-term placebo-controlled studies in depressive patients. In patients specifically diagnosed as bipolar (n = 158), the incidence of maniform states was 51% in 49 patients treated with imipramine alone, 21% in 60 patients treated with lithium alone, 28% in 36 patients treated with lithium and imipramine, and 23% in 13 patients receiving only placebo.

In our switch study, we collected the data from the records and investigated the switch rate of 158 bipolar I depressive inpatients of the Psychiatric University Hospital, Munich (Bottlender et al. 1998). In addition, we used the sociodemographic, anamnestic and psychopathological data from our routine documentation system (see above). Thirty-nine patients (25%) of the sample switched to a maniform state during the treatment period in the hospital. Among that group, the phenomenon occurred in 23 patients (15% of the total sample) as a hypomania and in 16 patients (10% of the total sample) as mania. This switch rate has to be interpreted under the aspect that the majority of the patients were treated with tricyclic antidepressants. Differentiating for the different kinds of antidepressants, the switch rate for TCA was 33.7%, for SSRIs 12% and for MAO inhibitors 8.3%. According to the naturalistic data set, mood stabilizers can reduce the risk of switching, especially in patients treated with tricyclics; however, the protection does not seem sufficient in all patients, since 59% of the switched patients received mood stabilizers. It is of great interest that apparently the switch into hypomania or mania has no significant influence on the duration of hospital treatment. However, under international perspectives, this finding is probably related to the long duration of hospital stay of about 60 days, which is not unusual for a

German university psychiatric hospital, and which demonstrates, on the one hand, the quite luxurious treatment conditions in German psychiatry and, on the other hand, gives a hint towards a selection of partially treatment refractory patients. The following variables were tested and not found to be significantly associated with the risk of switching: gender, age, duration of illness, number of prior episodes of mania, number of prior episodes of depression, severity of the depressive syndrome at admission, hallucinatory syndrome at admission. However, low basal TSH serum levels appeared to be a risk factor for switches into hypomanic/manic states (Bottlender et al. 2000a).

Contradictory to such findings, which show a link especially between treatment with tricyclic antidepressants and switch into mania/hypomania on the basis of a retrospective analysis of patient records, Lewis and Winokur (1982) found that a switch into mania occurred in 23 % of patients when tricyclics were used, and in 34 % of patients when no treatment was given. Based on these findings the authors concluded that tricyclics do not increase the risk of switching into mania, and that the so-called switch effect due to tricyclics represents random manifestations of bipolar illness. Angst's (1985) findings concerning patients admitted to the Zurich psychiatric university hospital between 1920 and 1982 go in the same direction. After the introduction of antidepressants in 1958, there was no significant increase of switches of unipolar or bipolar patients compared to the earlier treatment periods.

The hypothesis that antidepressants can induce switch into hypomania/mania is closely related to the hypothesis that antidepressants can induce rapid cycling (Wehr and Goodwin 1979a), and possibly also mixed states (Akiskal and Mallya 1987). In a retrospective study published by Altshuler et al. (1995), the longitudinal course of 51 patients with treatment refractory bipolar disorders was examined. The switch rate of patients in depressive episodes undergoing antidepressant treatment was 35 %. Cycle acceleration was likely to be associated with antidepressant treatment in 26 % of the patients.

Another naturalistic study described an increase of the frequency of episodes up to the rapid cycling phenomenon (> 4 episodes per year) under antidepressant treatment (Ghaemi et al. 1998). This tendency to an increased frequency of episodes was also found in some other studies (Reginaldi et al. 1982; Tondo et al. 1981; Wehr et al. 1988; Wehr and Goodwin 1979a).

Several authors (Kukopulos et al. 1980; Wehr and Goodwin 1979b) concluded that the best treatment against rapid cycling is the immediate withdrawal of the antidepressant medication.

However, there are also critical findings. Coryell et al. (1992) compared 919 patients with and without rapid cycling. The rapid cyclers were more frequent in those patients of female gender, with a depressive index episode or with an initial hypomania I fast switch from depression to hypomania. A causal relationship between the use of antidepressants and rapid cycling could not be demonstrated in this sample. To explain the results of other authors concerning the risk of antidepressants for inducing rapid cycling, the authors state that rapid cycling is significantly more often preceded by depression, which leads to therapy with an antidepressant, which leads in the end to the wrong causal attribution between antidepressant therapy and rapid cycling.

To summarize: there is a large body of evidence that antidepressant treatment can induce a switch into hypomania or mania (Grunze et al. 1999). According to recent studies, the risk of switching into hypomania/mania is lower than described in earlier studies. It apparently amounts to about 10–30 % under tricyclics, depending on the sample selection. Seemingly, tricyclics have the highest risk of inducing switch phenomena, while the risk under MAO inhibitors, and especially SSRIs, seems to be lower, for example, in the range of about 4–12 % for SSRIs. Lithium and other mood stabilizers apparently have a protective effect concerning the antidepressant-induced switch risk.

There is empirical evidence for a special risk of rapid cycling under antidepressant treatment. Due to the open and naturalistic manner of the studies, the results are not totally clear and leave some questions unanswered. If the induction of switching into mania and the induction of rapid cycling are related phenomena, it could be supposed that drugs like the tricyclics with a higher risk rate of inducing switch into mania also have a higher risk rate concerning rapid cycling. Altogether, argument 1 seems meaningful.

Argument 2: The risk of suicidality, suicide attempts and suicide in bipolar depressive patients is of minor clinical relevance.

It is common clinical knowledge that suicidality is a frequent problem in depressed patients, which can lead to severe damage in the case of suicide attempts, or even to a fatal outcome in the case of suicide. Guze and Robins (1970) were the first to review the extent of suicide risk in primary affective disorders, collecting data from studies available at the time. In nine studies on patients who were diagnosed as having manic depressive illness according to the diagnostic rules applicable at that time, 12 % to 19 % of deaths were due to suicide, and in eight studies the suicide rate ranged from 35 % to 60 %. The reviewers concluded that by the time all the patients in the studies they had examined had died, about 15 % would have committed suicide, which would make the rate in manic-depressive illness at least 30 times higher than that in the general population. In 1990, Goodwin and Jamison found in a review of 30 studies that 19 % of the patients with manic depressive illness had died due to suicide.

An adequately calculated lifetime risk of suicide would be estimated by following cohorts until all members of the cohort are dead. The data mentioned are not based on such sophisticated studies, which have not been performed hitherto on an adequately defined cohort of patients suffering from an affective illness. Nevertheless, a lifetime suicide risk of 15 % for patients with primary affective illness or major depression has been widely accepted for decades, based on the studies mentioned above.

More recent studies with a more sophisticated epidemiological methodology and the inclusion of computerized modeling techniques, for example, the study by Inskip et al. (1998), resulted in a lower risk rate. Inskip et al. (1998) selected 27 mortality studies of affective disorder from an earlier meta-analysis which assessed the suicide risk in all mental disorders (Harris and Barraclough 1997) and used mathematical modeling techniques to re-assess the lifetime risk of suicide in patients with affective disorder. The lifetime risk of suicide in affective disorder was estimated at 6 %. Higher percentages of suicide risk are seen soon after the onset of the disorder, when only a small proportion of the cohort has died: for example, when only 10 % of the cohort had died, suicide accounted for 27 % of the deaths.

The discrepancy between this comparatively low suicide rate and the usually quoted rate of 15 % may partially be the result of sampling biases (Simpson and Jamison 1999). For example, most of the earlier studies on suicide risk were based on severely depressed inpatients, while the great majority of patients with major depression are treated as outpatients. Some of the earlier studies also focus on patients with endogenous or melancholic features, who are at higher risk of suicide.

Most of the studies on the suicide risk of affective disorder did not distinguish between unipolar and bipolar disorder. It is an open question whether the suicide risk for bipolar patients is similar to that of unipolar patients (Lester 1993). The findings in the literature are conflicting. In a record-linkage, follow-up study on about 2000 patients with affective disorder, Black et al. (1988) found a lower suicide rate for bipolar patients compared to unipolar patients. This result was generally supported by two long-term follow-up studies of former inpatients (Angst et al. 1979**;** McGlashan 1984a), a follow-up study of 500 outpatients (Martin et al. 1985), and a case-control study (Winokur and Black 1987). Contrarily, two other studies reported a higher suicide risk for bipolar suicides than for unipolar suicides (Dunner et al. 1976**;** Morrison 1982). Four other studies reported similar risks in unipolar and bipolar affective disorders (Fawcett et al. 1987**;** Perris and d'Elia 1966**;** Tsuang 1978**;** Weeke and Vaeth 1986). Apparently, different designs and methods, in particular also sampling biases – e. g., inpatients versus outpatients, proportion of manic index episodes compared to depressive index episodes – are possible reasons for the different results.

A meta-analysis of suicide risk among patients with bipolar disorder, based on a combined population of 3700 bipolar patients from 14 studies in seven countries (Table 1), was performed by Harris and Barraclough (1997). The researchers also tried to avoid overestimating suicide risk, among others by not including papers with less than a minimum of a two year follow-up, and by excluding those publications reporting more than 10 % loss of subjects at follow-up. Based on these data, the total suicide risk was estimated to be 15 times higher than expected. At special risk were, among others, bipolar patients with a history of suicide attempts and with co-morbid alcohol abuse, and patients recently discharged from hospital. Sharma and Markar (1994) also found that suicide was a major cause of mortality early in the course of bipolar illness, with the mortality ratio for suicide being 23.4 times higher than in the general population: 15.7 % of patients died from suicide compared to only 0.67 % expected suicides.

The risk rates for suicide attempts are much higher than those for suicide. At least 25 % to 50 % of patients with bipolar disorder attempt suicide at one or more times in their lifetime (Goodwin and Jamison 1990). Commonly, suicide attempts/parasuicide are seen as less problematic than suicide. This is basically true, by definition. However, the relevance of suicide attempts, especially severe suicide attempts, should not be underestimated, given the fact that at least severe suicide attempts can lead to severe damage resulting in a life-long, embarrassing handicap.

Table 1 Suicide in bipolar disorder* (Simpson and Jamison 1999; for literature see source)

Report	Date	Country	Suicides (N)	
			Observed	Expected
Angst	1986	Switzerland	13	1.36[a]
Black et al.	1987	USA	7	0.48
Bratfos and Haug	1968	Norway	4	0.09
Carlson et al.	1974	USA	2	0.03[a]
Coppen et al.	1991	England	0	0.12
Dunner et al.	1976	USA	8	0.06[a]
Friis et al.	1991	Norway	2	0.02[a]
Kay and Petterson	1977	Sweden		
		Prelithium	3	0.41[a]
		Postlithium	0	0.15[a]
Lundquist	1945	Sweden	18	1.00[a]
Müller-Oerlinghausen et al.	1992	Germany	3	0.05[a]
Newman and Bland	1991	Canada	19	1.38
Noreik	1975	Norway	6	0.14[a]
Perris and d'Elia	1966	Sweden	3	0.23
Tsuang	1978	USA	5	0.66

* Standardized mortality ratio = 1505 (95 % CI, 1225–1844), total observed suicides = 93; expected total suicides = 6.18.
[a] Expected mortality ratio calculated by the authors.

Based on the data of the Epidemiologic Catchment Area (ECA) study, Chen and Dilsaver (1996) calculated the lifetime rates of suicide attempts among patients with bipolar and unipolar disorders. Lifetime rates of suicide attempts were 29.2 % in bipolar disorder, 15.9 % in unipolar disorder, and 4.2 % in all other DSM-III-defined axis I disorders. The odds ratio of patients with bipolar disorder having a history of suicide attempt relative to subjects in the control group was 6.2; the respective odds ratio for patients with unipolar disorder was 3.1 %. It was hypothesized that the higher rate of suicide attempts in bipolar patients may be related to the adverse developmental effects of an early age of onset, longer duration of illness and deterioration of hope due to an earlier mean age of onset, total number of episodes of affective illness, and the frequency of episodes.

The findings from the ECA study are in concordance with two follow-up studies on patients with affective disorders, which found a higher incidence of attempted suicide in bipolars, and are opposed to one study which found a higher incidence of attempted suicide in unipolars (Coryell et al. 1987**;** Dunner et al. 1976**;** McGlashan 1984a**,** 1984b).

In our own study on about 4500 inpatients (episodes of inpatient treatment) suffering from a unipolar or bipolar depression (according to ICD–9), suicidality of every kind was very frequent according to the respective item of a comprehensive rating instrument, the AMDP system (Association for Methodology and Documentation in Psychiatry) (Bottlender et al. 2000b). There were no significant differences between bipolar and unipolar depressive patients: 39 % of the bipolar and 38 % of the unipolar patients suffered from minor to major suicidal problems.

Suicidal behavior of bipolar patients is usually assumed to be associated with the depressive phase of the illness rather than with mania. This general clinical view is also supported by recent studies (Dilsaver et al. 1994**;** Isometsa et al. 1994). Of 31 bipolar I patients in the Finnish suicide study (Isometsa et al. 1994), suicide occurred during a major depressive episode in 79 % of the patients. The risk of suicidal behavior in mania, especially pure mania, is quite low. For example, the risk was 11 % in psychotic mania in the Finnish study. In the study by Dilsaver et al. (1994), suicidality of 93 patients who met the Research Diagnostic Criteria for bipolar disorder were rated by using the Schedule for Affective Disorders in Schizophrenia (SADS) suicide subscale. Only 2 % of the 49 patients who had pure mania were suicidal, compared to 55 % of the 34 patients with depressive (mixed) mania, thus, demonstrating that mixed states have a much higher risk than pure mania.

Based on their psychological autopsy study on suicide by patients suffering from a unipolar or bipolar disorder, Isometsa et al. (1994) came to the conclusion that suicides seem to occur significantly earlier in the course of bipolar illness among males than among females, and the proportion of late suicides in bipolar disorders is higher than previously thought. Co-morbid alcohol dependence was common among male but not female bipolar suicide victims. Bipolar suicide victims differed from the unipolar victims mainly in marital status (greater proportion of divorces) and treatment history (more frequent contacts). The majority of completed suicides in both bipolar and unipolar affective disorders seemed to be associated with recent psychological stress; however, the stresses (life events) are commonly likely to be dependent on the victim's behavior (Isometsa et al. 1995).

There is a great body of evidence that the treatment with antidepressants in an acute depressive episode not only leads to the remission of depressive symptoms of every kind, but also reduces suicidality (Möller 1992a**,** 1994**,** 1995**;** Möller and Steinmeyer 1994). As to tricyclics, the time course of the latter effect seems to follow the time course of the evaluation of depression, while selective serotonin re-uptake inhibitors (SSRIs) possibly have an earlier onset of the antisuicidal effect compared to the general antidepressive effect. However, this point is not consistent in the literature (Montgomery et al. 1981**;** Möller and Steinmeyer 1994**;** Muijen et al. 1988). In our own naturalistic study, mentioned above, on unipolar and bipolar patients undergoing treatment with antidepressants of several kinds, a remarkable reduction of suicidality, assessed with the respective item of the AMDP system, was observed. Altogether, there is no question that antidepressants exhibit not only a general antidepressive effect but also an antisuicidal effect in the acute phase of depression.

Similar data concerning the acute phase of depression are not available for the mood stabilizers. However, based on naturalistic studies, the finding that lithium reduces the frequency of suicide and suicide attempts during long-term treatment of unipolar or bipolar patients is becoming more and more robust. This antisuicidal effect is apparently not only associated with the relapse-preventing effect, but seems to a certain degree to be an effect of its own (Baldessarini et al. 1999**;** Müller-Oerlinghausen et al. 1992**,** 1996**;** Tondo et al. 1998). Apparently this antisuicidal effect, like the prophylactic effect, needs time to develop. The majority of data concerns patients who were treated with lithium for at least two years (Simpson and Jamison 1999). In contrast to these more robust findings, not much is known about the effects of other mood stabilizers on suicidal behavior. Hitherto, there are no clear hints that carbamazepine or valproate have an acute or long-term antisuicidal effect in unipolar or bipolar patients (Thies-Flechtner et al. 1996).

Undertreatment seems to be a great problem in bipolar patients who have committed suicide (Rihmer et al. 1990**;** Schou and Weeke 1988), as indicated in particular in the study by Isometsa et al. (1994). They found that although three quarters of the bipolar victims in their study were receiving psychiatric care at the time of death, the treatment that victims had received for the current illness episode was only adequate in some cases. Although lithium was indicated for all of the 31 persons with bipolar disorder, only one third were taking lithium, half with suboptimal serum levels, and poor compliance was reported for all but three. Of the depressed bipolar victims, only about one half were receiving antidepressants, and only a small minority (11 %) at probably adequate doses. The authors concluded that most suicides of persons with bipolar disorder seem to oc-

cur in cases in which adequate treatment for the current illness episode is not received or is inadequate.

The importance of adequate drug treatment of unipolar or bipolar depressive patients with suicidal tendencies was pointed out recently in the review by Hartmann (1996). He suggested that depressed patients with suicidal tendencies should be closely monitored and given full doses of antidepressant medications. The SSRIs lessen suicidal tendencies and, importantly, are markedly safer than the tricyclic antidepressants. Furthermore, they are less likely to cause rapid cycling in bipolar disorder.

To summarize: the risk of suicidal behavior associated with bipolar depression is substantial and of greatest clinical importance. The group of bipolar patients at highest risk of suicide are young men who are in the early course of their illness, especially those who have previously attempted suicide, those abusing alcohol, and those recently discharged from the hospital. As to bipolar disorders in general, the risk of suicide is greatest in bipolar depression and mixed states, but very low in pure manic states. Antidepressants reduce suicidality in a similar time course as they reduce depressive symptoms. SSRIs may possibly have a faster onset of the antisuicidal effect. In addition, they are much safer with respect to overdosing. Lithium appears to provide protection against suicidal behavior under long-term treatment conditions, an effect which was not demonstrated for other mood stabilizers like carbamazepine or valproate. Generally, patients with acute bipolar depression should be treated with antidepressants to reduce the risk of suicide attempts or suicide.

Altogether, argument 2 does not concur with the high frequency of suicidality in bipolar depression and its severe clinical, psychosocial and often fatal outcome.

Argument 3: The antidepressive efficacy of antidepressants in bipolar depression is insufficiently proven

Antidepressants were extensively studied in patients with unipolar depression and in mixed groups of patients with unipolar and bipolar disorder during the first few decades after the introduction of the tricyclic antidepressants. At that time, the efficacy of antidepressants in episodes of acute bipolar depression was not generally evaluated separately. For a long time it did not seem relevant or necessary to prove the efficacy of antidepressants in separate samples of bipolar depression. However, the situation is currently changing and arguments have been made that this view possibly does not hold true (Hirschfeld et al. 1994; Sachs 1996) and that the efficacy of antidepressants in bipolar depression has to be questioned. In this context, differences in the underlying biological processes in unipolar and bipolar depression should be mentioned (Soares and Mann 1997; Souery et al. 1996).

Proceeding from this position, over the last few decades bipolar depressive patients were excluded from phase II and phase III studies testing the efficacy of the newer antidepressants, to restrict variance of the efficacy data and to avoid the risk of switch and rapid cycling phenomena. In addition, this led to a small number of controlled trials on antidepressants in samples of acute bipolar depressive patients (Baumhackl et al. 1989; Cohn et al. 1989; Katz et al. 1987; Zornberg and Pope Jr 1993).

Apparently, the skeptical view that antidepressants might not be effective in acute bipolar depression, which seems to be very extreme, or the position that they might not be as effective as in unipolar depression, or that the induced risk of switch into mania and rapid cycling might override the benefits of a good antidepressive response, which were expressed in this very skeptical and maybe over-critical tendency especially in the last few years, is not supported by empirical evidence.

Zornberg and Pope (1993) reviewed seven controlled studies that examined the efficacy of tricyclic antidepressants in the treatment of bipolar depression. In general, the data indicate that tricyclic antidepressants are more effective than placebo for patients with bipolar depression. The relative efficacy compared to other antidepressants is not so clearly established. Their efficacy when combined with lithium or alternatively with mood stabilizers has not been systematically studied, although this is the manner in which antidepressants are increasingly used in acute bipolar depression. Two controlled studies have tested monoaminoxidase inhibitors in patients with bipolar depression. One study found the reversible MAOA inhibitor moclobemide to be equivalent to imipramine in a heterogeneous group of depressed patients, including 33 bipolar patients (Baumhackl et al. 1989). The other study showed that the classical MAO inhibitor tranylcypromine was significantly superior to imipramine in the anergic subtype of bipolar depression in patients with bipolar I and bipolar II disorder (Himmelhoch et al. 1991). SSRIs have not been well studied in a controlled manner in the treatment of acute bipolar depression. One controlled study found that fluoxetine was superior to imipramine and placebo in the treatment of acute bipolar depression (Cohn et al. 1989). Two clinical trials suggested buproprione as effective in the treatment of episodes of bipolar depression (Fogelson et al. 1992; Sachs et al. 1994).

All of these studies have methodological limitations: most of them were conducted in only a small number of patients, a placebo control group was rarely used, and the risk and especially differential risk of a switch into mania was apparently of greater interest in some of the studies than the proper evaluation of the antidepressive efficacy. Nevertheless, altogether the data appear to support to a certain degree the hypothesis that antidepressants are effective not only in acute unipolar depression but also in acute bipolar depression.

It has to be admitted, as already pointed out, that the database from controlled clinical trials is limited. Nevertheless, it gives no hint that antidepressants might not be effective in acute bipolar depression. Under this aspect, it seems questionable whether we really need more formal studies on the efficacy of classical or new generation antidepressants in bipolar disorders, with all the associated risks for the patients, or whether we should continue to be-

lieve in the traditional hypothesis that a drug which has shown efficacy in unipolar depression is also effective in bipolar depression. Based on the theoretical assumption that most psychoactive drugs are syndrome-orientated in their efficacy and not cause related, we not only suppose the efficacy of antidepressants in unipolar as well as in bipolar functional depression but even in organic depression. Especially the broad clinical experience from many years of treatment with antidepressants seems to validate this approach. Therefore, in the following section our own study based on controlled clinical experiences in the routine treatment conditions of a large sample of inpatients, which definitely shows that acute bipolar depressive patients respond as well as acute unipolar depressive patients, will be presented. The results are even more convincing because, given the fact that the sample was an inpatient sample, most of the patients suffered from a severe unipolar or bipolar depression. Thus, we avoided the uncertainty which is a risk when studying antidepressive efficacy in mild or moderate depression, where it has been shown that anxiolytics or other drugs can also turn out as "antidepressants" (Laakman et al. 1986**;** Laakman et al. 1995**;** Möller et al. 1991).

In this study (Möller et al. 1999), the data from 2032 inpatients with unipolar or bipolar I depression, who had been consecutively admitted to the Psychiatric University Hospital, Munich, were compared concerning efficacy of antidepressants in both groups under naturalistic treatment conditions. The outcome was assessed by the Global Assessment Scale (GAS), the duration of hospitalization, and the depression, apathy and mania syndrome subscale of a comprehensive rating instrument, the AMDP system (AMDP = Association for Methodology and Documentation in Psychiatry) (AMDP System 1982**;** Pietzcker et al. 1983). The study is based on the routine documentation in the Psychiatric University Hospital in Munich, which has been performed since the late 1970s and which includes sociodemographic data, anamnestic data, treatment and psychopathological data. In those patients with multiple hospitalizations, only the first stay in our hospital was considered for this study. Due to the fact that the cohort under investigation was treated in the years 1980 to 1992, the great majority of the patients were treated with tricyclics or tetracyclics, monoaminoxidase inhibitors were administered to a much lesser degree, while SSRIs were seldom used.

The cohorts of unipolar and bipolar depressive patients were comparable with respect to psychosocial parameters, the severity of depression at admission and treatment regimens. At discharge, there were no statistically significant differences between bipolar I and unipolar depression for the outcome criteria depressive syndrome, GAS score and days in hospital. Bipolar patients showed a slightly decreased apathy score at discharge, and a slightly elevated score of the manic syndrome. In addition to the main analysis on the outcome of unipolar and bipolar depressed patients, several additional analyses were performed:

- Outcome in unipolar and bipolar depressed patients subdivided into four year cohorts (1980–1984, 1985–1988, 1989–1992), reflecting potential changes in treatment regimens.
- Outcome in unipolar and bipolar depressed patients grouped for different degrees of severity of depression.
- Outcome in unipolar and bipolar depressed patients for different age groups.
- Outcome in unipolar and bipolar depressed patients for different gender groups.
- Outcome in unipolar and bipolar depressed patients with and without neuroleptic treatment as add-on to antidepressant treatment.

None of these sub-analyses revealed any significant differences between the response of unipolar or bipolar depressed patients, and especially there was no difference between more or less severely depressed groups of patients.

These results seem to reject the hypothesis that antidepressants – in the case of this study predominantly tricyclics – may be less effective in the acute treatment of bipolar I depressed patients compared to unipolar depressed patients. The large sample size of this study supports a high validity of this conclusion. This study did not check for differences in unwanted effects, such as switching or rapid cycling, which are commonly attributed to the use of tricyclics antidepressants in bipolar patients. Apparently these unwanted effects, for which data are available from a subgroup of 158 bipolar I depressed patients (Bottlender et al. 1998), did not lead to a prolongation of the average duration of the hospital stay in the bipolar patients compared to the unipolar patients.

To summarize, when all the evidence is taken together, there does not seem to be any question that antidepressants are effective in acute bipolar I depression, and that apparently the efficacy is equal to the response in unipolar depression. The argument that the antidepressive efficacy of antidepressants in bipolar depression is insufficiently proven is apparently a very formalistic argument, which has its background in the unproven hypothesis that antidepressant treatment is disease-specific and must be tested in each specific disease entity. However, it is much more likely that antidepressant treatment is syndrome oriented and that antidepressants are effective in functional depression of the unipolar or bipolar subtype (as well as in exogenous depression). An overwhelming amount of clinical experience seems to confirm this hypothesis.

Apart from this positive statement for the use of antidepressants in bipolar depression, it should be considered that the use of antidepressants has its special limitations in bipolar depressions in rapid cycling conditions, and also in mixed mania or mixed depression. In the case of rapid cycling, treatment with an antidepressant should be generally stopped soon after remission to avoid the induction of further rapid cycling. In mixed mania/mixed depression, antidepressants have to be avoided because they are contra-indicated in the presence of manic symptoms (Calabrese and Woyshville 1995**;** Sachs 1996). In cases of acute bipolar depression with psychotic symptoms like delusions etc., co-medication with a neuroleptic is necessary in most cases.

Argument 4: The antidepressive efficacy of mood stabilizers in bipolar depression is sufficiently proven

Several experts and guidelines recommend mood stabilizers as the treatment of first choice in acute bipolar depression (Frances et al. 1996, 1998; Hirschfeld et al. 1994; Sachs 1996; Yatham et al. 1997). This recommendation has to be questioned as long as there is no definite proof that mood stabilizers have antidepressive efficacy in unipolar and/or bipolar depression, and that this efficacy is comparable to the antidepressive efficacy of traditional or modern antidepressants.

Traditionally, lithium is the most intensively evaluated mood stabilizer with respect to antidepressive efficacy (Adli et al. 1998; Mendels 1976; Souza and Goodwin 1991). In controlled studies, lithium showed a certain antidepressive activity. Altogether, the total number of patients included in these studies is very small. In most studies, no differentiation is made between unipolar and bipolar depression. Several of the controlled studies are not randomized, parallel group studies, but followed cross-over designs with all their known problems and limitations, including the problem of hangover and withdrawal phenomena. Most of the randomized, parallel group studies compare lithium with a standard antidepressant, without a placebo arm. The sample size is extremely low 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 fact of an enormous ß-error problem. Furthermore, in most of the studies the daily dose of the standard comparator was inadequate, e. g. 100 mg/day of a tricyclic or less. Without mentioning the other methodological problems from a modern perspective, the essence of these studies with respect to efficacy is extremely weak, a critical position which can not 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, the power strength of the antidepressive effects compared to antidepressants is widely unclear but generally the data 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). A recent study presented by Nemeroff et al. (1997), in which the combination of lithium with placebo, with paroxetine and with imipramine in the treatment of bipolar depression were compared under double-blind conditions, demonstrated that co-medication with an antidepressant led to a significantly higher responder rate compared with monotherapy with lithium. To avoid misunderstandings, these statements are only related to the question of acute antidepressive effects of lithium and not to the efficacy of lithium augmentation.

The respective database giving hints of an antidepressive property of carbamazapine is even worse. 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 depressives, found a response rate of 56 % for depressed patients in open trials and 44 % for patients in the controlled studies (moderate and good response) (Post et al. 1997). Apparently, the responder rates between unipolar and bipolar depressive patients are not different, as demonstrated in the studies of Svestka et al. (1991) and Dilsaver et al. (1996), for example. In two double-blind studies (Ballenger and Post 1980; Post et al. 1986), evidence for a good treatment response was not found in patients under carbamazepine mono-therapy.

As to valproate, the database is even weaker. In an open study, Calabrese and Delucchi (1990) found a marked improvement in 57 % of the patients. In the study with the largest sample of 103 patients, however, a moderate improvement was only found in 22 % of the patients (Lambert 1984).

With respect to the current methodological standards in the field of the evaluation of antidepressive efficacy of mood stabilizers, 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 an antidepressive property of lamotrigine. In this study, 200 mg lamotrigine per day was compared to 50 mg lamotrigine per day and to placebo. Lamotrigine 200 mg/day demonstrated antidepressant efficacy on different outcome parameters like the total score of the Hamilton Depression Scale (HAM-D), the total score of the Montgomery-Asberg Depression Rating Scale (MADRS), the score of the item depressive mood of the HAM-D and the Clinical Global Impressions (CGI) compared to placebo. Lamotrigine 50 mg/day demonstrated some efficacy compared to placebo but was inferior to the higher dosage of lamotrigine. Responder rates (CGI) were 51 % in the lamotrigine 200 mg/day group, 41 % in the 50 mg lamotrigine group and 26 % in the placebo group. These positive findings need replication, hopefully, in a three-arm study comparing 200 mg/day lamotrigine with placebo and an antidepressant, preferentially an SSRI or another modern antidepressant known for a low switch-rate risk. Under tactical aspects it should be mentioned that lamotrigine must be increased very slowly, due to its known risk of severe dermatosis, not reaching the final dose of 200 mg/day before 6 weeks. This might limit the possibility of inducing an antidepressive response as soon as possible.

To prove the antidepressive efficacy of lithium or other mood stabilizers, at least two adequately designed, positive, double-blind, randomized, parallel group studies in comparison to placebo are necessary. In trials comparing a mood stabilizer to standard antidepressants, the ß-error problem has to be considered very carefully before the conclusion of equal efficacy can be made. The antidepressive property of mood stabilizers has to be proven in severe depression before a final judgement on the antidepressive efficacy can be made (Laakman et al. 1986; Montgomery and Lecrubier 1999; Möller 1992b).

To summarize: overall the antidepressive efficacy of

mood stabilizers is not well proven, at least not following the same methodological standards as are commonly used for establishing the efficacy of antidepressants. Although there are some hints for an antidepressive efficacy of mood stabilizers, especially for lithium, and also for lamotrigine, the question remains open whether this antidepressive efficacy is comparable to that of antidepressants. There are at least some data showing a lower efficacy of lithium compared to antidepressants or the co-medication of lithium with antidepressants. Especially this question needs further evaluation before a final conclusion can be drawn whether antidepressants should be replaced by lithium or other mood stabilizers 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 stabilizers also has to be taken into consideration. Some of the mood stabilizers have an unfavorable side-effect profile, at least compared to modern antidepressants.

In all, argument 4, that the antidepressive efficacy of mood stabilizers in bipolar depression is sufficiently proven, must be rejected.

Discussion

As shown in this critical review, the risk of mania and risk of rapid cycling induced by antidepressants has been overestimated in comparison to the risk of suicidal behavior. Of course, it is difficult to make the right decision between Scylla and Charybdis. Nevertheless, suicidality seems to be the more critical outcome. Coming from this position the question has to be posed: Have we lost a well-balanced view concerning the use of antidepressants in acute bipolar depression?

The general need of antidepressant treatment in bipolar depression, at least in moderate and severe cases, has to be stressed in this context to avoid the risk of suicidal behavior and chronic depression (Hlastala et al. 1997). To date, there are no data available which show comparable efficacy of drugs other than antidepressants in acute bipolar depressive patients. The opposite is true – most of the mood stabilizers have not been investigated in an adequate way, i. e., in double-blind, randomized, parallel group studies in comparison to placebo and/or standard antidepressants in acute unipolar or bipolar depression, and the evidence of antidepressive efficacy is generally weak.

Most experts' recommendations and guidelines differentiate between different classes of antidepressants concerning the risk of inducing mania. There seems a broad consensus that SSRIs, and possibly other modern antidepressants, have a much lower risk than the tricyclics, possibly close to that of placebo. If this holds true, is it really acceptable that the treatment recommendations are so restrictive concerning the use of modern antidepressants as mentioned above? As recommended in some of the guidelines, the SSRIs or possibly other modern antidepressants, should be the first choice in the treatment of acute bipolar depression.

In spite of the lack of evidence of efficacy, some modern treatment guidelines define mood stabilizers as the first line treatment in acute bipolar depression. It should be generally considered that mood stabilizers are neither licensed by the US-American nor by the European drug authorities for the indication acute bipolar depression. Under this aspect, the recommendation of mood stabilizers in acute bipolar depression is quite an unusual situation, meaning, among other things, that these treatment guidelines might be very premature and not covered by the official regulations of the drug authorities, and therefore have a risk of insurance problems, among others, for example, if a patient suffering from an acute bipolar depression commits suicide without having had the chance to receive proper treatment with antidepressants. All experts and consensus groups should take this aspect into serious consideration.

The recommendation that antidepressants should be used in co-medication with a mood stabilizer, common in most of the recommendations and guideline papers, seems plausible and clinically meaningful. However, as described before, the databases for this recommendation need additional studies. Of greatest importance is the question when the antidepressant should be withdrawn. In some of the guidelines, there is the tendency to withdraw the antidepressant as soon as possible, e. g., after 6–12 weeks (Sachs 1996). This proposal is in contrast to the convention – accepted up to now at least for the treatment of unipolar depression – that a continuation therapy of 6, or better 12 months is necessary to avoid early relapse. Apparently, the divergent recommendation for bipolar disorders is again based on an over-consideration of the risk of inducing mania compared to the risk of inducing relapse, and on the other side on the assumption, which is not proven at all, that a mood stabilizer might be effective enough in the continuation phase to avoid early relapse of depression. A more classical and possibly more effective approach would be to continue the co-medication of a mood stabilizer and an antidepressant for at least 6–12 months, with the exception of rapid cycling patients. Although this strategy has not been tested sufficiently, at least the available data seem to give the impression that the risk of inducing mania is markedly reduced by this co-medication with lithium.

References

Adli M, Bschor T, Canata B, Dopfmer S, Bauer M (1998) [Lithium in the treatment of acute depression]. Fortschr Neurol Psychiatr 66: 435–441

Akiskal HS, Mallya G (1987) Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 23: 68–73

Akiskal HS, Djenderedjian AM, Rosenthal RH, Khani MK (1977) Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 134: 1227–1233

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L (1995) Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 152: 1130–1138

AMDP System (1982) Association of Methodology and Documentation in Psychiatry: Manual for the Assessment and Documentation of Psychopathology. Springer, Berlin

Angst J (1985) Switch from depression to mania – a record study over decades between 1920 and 1982. Psychopathology 18: 140–154

Angst J, Felder W, Frey R (1979) The course of unipolar and bipolar affective disorder. In: Schou M, Stromgen E (eds) Origin, Prevention and Treatment of Affective Disorders. London, Academic Press, pp 215–26

Baldessarini RJ, Tondo L, Hennen J (1999) Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 60 Suppl 2: 77–84

Ballenger JC, Post RM (1980) Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 137: 782–790

Bauer MS, Callahan AM, Jampala C, Petty F, Sajatovic M, Schaefer V, Wittlin B, Powell BJ (1999) Clinical practice guidelines for bipolar disorder from the department of veterans affairs. J Clin Psychiatry 60: 9–21

Baumhackl U, Biziere K, Fischbach R, Geretsegger C, Hebenstreit G, Radmayr E, Stabl M (1989) Efficacy and tolerability of moclobemide compared with imipramine in depressive disorder (DSM-III): an Austrian double-blind, multicentre study. Br J Psychiatry 155 (Suppl 6): 78–83

Black DW, Winokur G, Nasrallah A (1988) Effect of psychosis on suicide risk in 1,593 patients with unipolar and bipolar affective disorders. Am J Psychiatry 145: 849–852

Boerlin HL, Gitlin MJ, Zoellner LA, Hammen CL (1998) Bipolar depression and antidepressant-induced mania: a naturalistic study. J Clin Psychiatry 59: 374–379

Bottlender R, Rudolf D, Strauss A, Möller HJ (1998) Antidepressant-associated maniform states in acute treatment of patients with bipolar-I depression. Eur Arch Psychiatry Clin Neurosci 248: 296–300

Bottlender R, Rudolf D, Strauss A, Möller HJ (2000) Are low basal serum levels of the thyroid stimulating hormone (TSH) a risk factor for switches to maniform states in bipolar I depression? Pharmacopsychiatry [In Press]

Bottlender R, Strauss A, Möller HJ (2000) Suicidality in bipolar and unipolar depressive inpatients. [In Preparation]

Bunney Jr WE (1978) Psychopharmacology of the switch process in affective illness. In: Lipton MA, Kellam KF (eds) Psychopharmacology: A generation of Progress. New York, Raven Press, pp 1249–59

Calabrese JR, Delucchi GA (1990) Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 147: 431–434

Calabrese JR, Woyshville MJ (1995) A medication algorithm for treatment of bipolar rapid cycling? J Clin Psychiatry 56 Suppl 3: 11–18

Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD (1999) A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 60: 79–88

Chen YW, Dilsaver SC (1996) Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol Psychiatry 39: 896–899

Cohn JB, Collins G, Ashbrook E, Wernicke JF (1989) A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 4: 313–322

Coryell W, Andreasen NC, Endicott J, Keller M (1987) The significance of past mania or hypomania in the course and outcome of major depression. Am J Psychiatry 144: 309–315

Coryell W, Endicott J, Keller M (1992) Rapidly cycling affective disorder. Demographics, diagnosis, family history, and course. Arch Gen Psychiatry 49: 126–131

Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Krajewski KJ (1994) Suicidality in patients with pure and depressive mania. Am J Psychiatry 151: 1312–1315

Dilsaver SC, Swann SC, Chen YW, Shoaib A, Joe B, Krajewski KJ, Gruber N, Tsai Y (1996) Treatment of bipolar depression with carbamazepine: results of an open study. Biol Psychiatry 40: 935–937

Dunner DL, Gershon ES, Goodwin FK (1976) Heritable factors in the severity of affective illness. Biol Psychiatry 11: 31–42

Fawcett J, Scheftner W, Clark D, Hedeker D, Gibbons R, Coryell W (1987) Clinical predictors of suicide in patients with major affective disorders: a controlled prospective study. Am J Psychiatry 144: 35–40

Fieve RR, Platman SR, Plutchik RR (1968) The use of lithium in affective disorders. I. Acute endogenous depression. Am J Psychiatry 125: 487–491

Fogelson DL, Bystritsky A, Pasnau R (1992) Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 53: 443–446

Frances AJ, Docherty JP, Kahn DA (1996) The Expert Consensus Guidelines for treating depression in bipolar disorder. J Clin Psychiatry 57 (Suppl 12A): 3–88

Frances AJ, Kahn DA, Carpenter D, Docherty JP, Donovan SL (1998) The Expert Consensus Guidelines for treating depression in bipolar disorder. J Clin Psychiatry 59 (Suppl 4): 73–79

Ghaemi SN, Lee-Cherry ER, Katzow JJ, Goodwin FK Olanzapine treatment in mood disorders. APA Annual Meeting Abstracts (1998) 151: NR 136

Goodwin FK, Jamison KR (1990) Manic-Depressive Illness. Oxford University Press, New York

Goodwin GM, Nolen WA (1997) Treatment of bipolar depressive mood disorders: algorithms for pharmacotherapy. Int J Psychiatry Clin Prac 1 (Suppl. 1): S9–S12

Grunze H, Schlösser S, Walden J (1999) Neue Perspektiven in der Akutbehandlung bipolarer Depressionen. Psychopharmakotherapie 6: 53–59

Guze SB, Robins E (1970) Suicide and primary affective disorders. Br J Psychiatry 117: 437–438

Harris EC, Barraclough B (1997) Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry 170: 205–228

Hartmann PM (1996) Strategies for managing depression complicated by bipolar disorder, suicidal ideation, or psychotic features. J Am Board Fam Pract 9: 261–269

Himmelhoch JM, Thase ME, Mallinger AG, Houck P (1991) Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 148: 910–916

Hirschfeld RMA, Clayton PJ, Cohen I, Fawcett J, Keck P, McClellan J, McElroy S, Post R, Satloff A (1994) Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Association. Am J Psychiatry 151: 1–36

Hlastala SA, Frank E, Mallinger AG, Thase ME, Ritenour AM, Kupfer DJ (1997) Bipolar depression: an underestimated treatment challenge. Depress Anxiety 5: 73–83

Inskip HM, Harris EC, Barraclough B (1998) Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry 172: 35–37

Isometsa ET, Henriksson MM, Aro HM, Lonnqvist JK (1994) Suicide in bipolar disorder in Finland. Am J Psychiatry 151: 1020–1024

Isometsa E, Heikkinen M, Henriksson M, Aro H, Lonnqvist J (1995) Recent life events and completed suicide in bipolar affective disorder. A comparison with major depressive suicides. J Affect Disord 33: 99–106

Kasper S, Haushofer M, Zapotoczky HG, Aschauer H, Wolf R, Hinterhuber H, Bonelli M, Wuschitz A (1999) Konsensus-Statement: Diagnostik und Therapie der bipolaren Störung. Neuropsychiatrie 13: 100–108

Katz MM, Koslow SH, Maas JW, Frazer A, Bowden CL, Casper R, Croughan J, Kocsis J, Redmond E (1987) The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychol Med 17: 297–309

Khan MC, Wickham EA, Reed JV (1987) Lithium versus placebo in acute depression: a clinical trial. Int Clin Psychopharmacol 2: 47–54

Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L (1980) Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol 13: 156–167

Kusumakar V, Yatham LN, Haslam DR, Parikh SV, Matte R, Silverstone PH, Sharma V (1997) Treatment of mania, mixed state, and rapid cycling. Can J Psychiatry 42 Suppl 2: 79S–86S

Laakman G, Blaschke D, Hippius H, Messerer D (1986) Alprazolam versus amitriptyline in the treatment of depressed out-patients: a randomized double-blind trial. In: Lader HL, Davies HC (eds) Drug treatment of Neurotic Disorders. Edinburgh London Melbourne New York, Churchill Livingstone, pp 129–36

Laakman G, Faltermaier TM, Bossert ZS, Baghai T, Lorkowski G (1995) Treatment of depressive outpatients with lorazepam, alprazolam, amytriptyline and placebo. Psychopharmacology Berl 120: 109–115

Lambert PA (1984) Acute and prophylactic therapies of patients with affective disorders using valpromide (dipropylacetamide). In: Emrich HE, Okuma T, Müller AA (eds) Anticonvulsants in Affective Disorders. Amsterdam, Elsevier Science Publishers, pp 33–44

Lester D (1993) Suicidal behavior in bipolar and unipolar affective disorders: a meta-analysis. J Affect Disord 27: 117–121

Lewis JL, Winokur G (1982) The induction of mania. A natural history study with controls. Arch Gen Psychiatry 39: 303–306

Martin RL, Cloninger CR, Guze SB, Clayton PJ (1985) Mortality in a follow-up of 500 psychiatric outpatients. II. Cause-specific mortality. Arch Gen Psychiatry 42: 58–66

McGlashan TH (1984a) The Chestnut Lodge follow-up study. I. Follow-up methodology and study sample. Arch Gen Psychiatry 41: 573–585

McGlashan TH (1984b) The Chestnut Lodge follow-up study. II. Long-term outcome of schizophrenia and the affective disorders. Arch Gen Psychiatry 41: 586–601

Mendels J (1976) Lithium in the treatment of depression. Am J Psychiatry 133: 373–378

Montgomery SA, Lecrubier Y (1999) Is severe depression a separate indication? ECNP Consensus Meeting September 20, 1996, Amsterdam. European College of Neuropsychopharmacology. Eur Neuropsychopharmacol 9: 259–264

Montgomery SA, McAuley R, Rani SJ, Roy D, Montgomery DB (1981) A double blind comparison of zimelidine and amitriptyline in endogenous depression. Acta Psychiatr Scand Suppl 290: 314–327

Morrison JR (1982) Suicide in a psychiatric practice population. J Clin Psychiatry 43: 348–352

Motohashi N (1999) Algorithms for the pharmacotherapy of bipolar disorder. Psychiatry and Clinical Neurosciences 53: S41-S44

Möller HJ (1992a) Antidepressants – do they decrease or increase suicidality? Pharmacopsychiatry 25: 249–253

Möller HJ (1992b) Klinische Prüfstudien. Allgemeine Grundlagen der Pharmakopsychiatrie. Riederer P, Laux G, and Pöldinger W. Neuro-Psychopharmaka. 1.Wien New York, Springer, pp 177–99

Möller HJ (1994) Einfluss von Antidepressiva auf die Suizidalität depressiver Patienten [The effect of antidepressive agents on suicide in depressive patients]. Fortschr Neurol Psychiatr 62 Suppl 1: 19–23

Möller HJ (1995) Suizidalität unter Antidepressivabehandlung. In: Wolferdorf M, Kaschka WP (eds) Suizidalität – Die biologische Dimension. Tropon-Symposium, Bd X. Berlin Heidelberg New York, Springer-Verlag, pp 129–39

Möller HJ, Steinmeyer EM (1994) Are serotonergic reuptake inhibitors more potent in reducing suicidality? An empirical study on paroxetine. Eur Neuropsychopharmacol 4: 55–59

Möller HJ, Riehl T, Dietzfelbinger T, Wernicke T (1991) A controlled study of the efficacy and safety of mianserin and maprotiline in outpatients with major depression. Int Clin Psychopharmacol 6: 179–192

Möller HJ, Bottlender R, Grunze H, Strauss A, Wittmann J (2000) Are antidepressants not or less effective in the acute treatment of bipolar I compared to unipolar depression? J Aff Disord [In Press]

Muijen M, Roy D, Silverstone T, Mehmet A, Christie M (1988) A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. Acta Psychiatr Scand 78: 384–390

Müller-Oerlinghausen B, Muser CB, Volk J (1992) Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord 25: 261–269

Müller-Oerlinghausen B, Wolf T, Ahrens B, Glaenz T, Schou M, Grof E, Grof P, Lenz G, Simhandl C, Thau K et al. (1996) Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the International Group for the Study of Lithium-treated patients (IGSLI). Acta Psychiatr Scand 94: 344–347

Nemeroff CB Treating depression in the bipolar patient. APA Annual Meeting Abstracts (1997) 150: 272

Peet M (1994) Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 164: 549–550

Perris C, d'Elia G (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. X. Mortality, suicide and life-cycles. Acta Psychiatr Scand Suppl 194: 172–189

Pietzcker A, Gebhardt R, Strauss A, Stöckel M, Langer C, Freudenthal K (1983) The syndrome scales in the AMDP system. In: Bobon D, Baumann U, Angst J, Helmchen H, Hippius H (eds) AMDP System in Pharmacopsychiatry. Basel, Karger, pp 88–99

Post RM, Uhde TW, Roy BP, Joffe RT (1986) Antidepressant effects of carbamazepine. Am J Psychiatry 143: 29–34

Post RM, Leverich GS, Denicoff KD, Frye MA, Kimbrell TA, Dunn R (1997) Alternative approaches to refractory depression in bipolar illness. Depress Anxiety 5: 175–189

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 41: 1096–1104

Quitkin FM, Kane J, Rifkin A, Ramos LJ, Nayak DV (1981) Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. A double-blind study. Arch Gen Psychiatry 38: 902–907

Reginaldi D, Tondo L, Caliari B, Minnai GP, Kukopulos A (1982) The role of antidepressants in rapid cyclicity. Adv Biochem Psychopharmacol 32: 363–367

Rihmer Z, Barsi J, Arato M, Demeter E (1990) Suicide in subtypes of primary major depression. J Affect Disord 18: 221–225

Rouillon F, Lejoyeaux M, Filteau MJ (1992) Unwanted effects of long-term treatment. In: Montgomery SA, Rouillon FA (eds) Long-term Treatment of Depression. New York, Wiley, pp 81–111

Sachs GS (1996) Bipolar mood disorder: practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol 16: 32S–47S

Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF (1994) A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 55: 391–393

Schou M, Weeke A (1988) Did manic-depressive patients who committed suicide receive prophylactic or continuation treatment at the time? Br J Psychiatry 153: 324–327

Sharma R, Markar HR (1994) Mortality in affective disorder. J Affect Disord 31: 91–96

Simpson SG, Jamison KR (1999) The risk of suicide in patients with bipolar disorders. J Clin Psychiatry 60 Suppl 2: 53–56

Soares JC, Mann JJ (1997) The anatomy of mood disorders – review of structural neuroimaging studies. Biol Psychiatry 41: 86–106

Souery D, Papadimitriou GN, Mendlewicz J (1996) New molecular genetic studies in affective disorders. In: Papamitrou GN, Mendelwicz J (eds) Genetics of Mental Disorders Part II: Clinical Issues. Bailliere's clinical psychiatry. Vol 2, No1. International practice and research. London, Bailliere Tindall, pp 1–13

Souza FG, Goodwin GM (1991) Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry 158: 666–675

Svestka J, Deskova E, Rysanek R, Nahunek K (1991) Antiepileptics in the treatment of endogenous depression. Proceedings IVth World Congress of Biological Psychiatry

Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W (1996) Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. Pharmacopsychiatry 29: 103–107

Tondo L, Laddomada P, Serra G, Minnai G, Kukopulos A (1981) Rapid cyclers and antidepressants. Int Pharmacopsychiatry 16: 119–123

Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M (1998) Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry 59: 405–414

Tsuang MT (1978) Suicide in schizophrenics, manics, depressives, and surgical controls. A comparison with general population suicide mortality. Arch Gen Psychiatry 35: 153–155

Walden J, Grunze H, Schlösser S, Berger M, Bergmann A, Bräunig P, Dose M, Emrich HE, Gastpar M, Greil W et al. (1999) Empfehlungen für die Behandlung bipolarer affektiver Störungen (Recommendations for the treatment of bipolar affective disorder). Psychopharmakotherapie 6: 115–123

Weeke A, Vaeth M (1986) Excess mortality of bipolar and unipolar manic-depressive patients. J Affect Disord 11: 227–234

Wehr TA, Goodwin FK (1979a) Rapid cycling between mania and depression caused by maintenance tricyclics. Psychopharmacol Bull 15: 17–19

Wehr TA, Goodwin FK (1979b) Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 36: 555–559

Wehr TA, Sack DA, Rosenthal NE, Cowdry RW (1988) Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 145: 179–184

Winokur G, Black DW (1987) Psychiatric and medical diagnoses as risk factors for mortality in psychiatric patients: a case-control study. Am J Psychiatry 144: 208–211

Yatham LN, Kusumakar V, Parikh SV, Haslam DR, Matte R, Sharma V, Kennedy S (1997) Bipolar depression: treatment options. Can J Psychiatry 42 Suppl 2: 87S–91S

Zornberg GL, Pope Jr HG (1993) Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 13: 397–408