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
the treatment of acute bipolar depression, i.e. to prescribe the most powerful antidepressive treatment (Bottinger 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-