REVIEW ARTICLE

The use of atypical antipsychotics in Bipolar Spectrum disorders

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ABSTRACT

Viewed in the context of ever-expanding conceptual boundaries for the diagnosis of bipolar disorder including the spectrum concept of DSM-IV, or even beyond (Akiskal and Pinto, 1999), it becomes obvious that lithium is the treatment of choice in a minority of patients only (Bowden et al, 2000). This article reviews what additional benefit atypical antipsychotics may provide in patients with bipolar disorder.

Due both to tradition and to the regulatory requirements in the USA (FDA) and European Union (EMEA), the main target of clinical trials with atypical antipsychotics has been typical manic disorder. More recently, a significant subgroup of atypical patients, e.g., with mixed states, marked psychosis, or rapid cycling, have participated in these studies to allow an estimation of the value of atypical antipsychotics in these conditions. For the purposes of filing applications for registration with the regulatory agencies, the existing evidence is probably weak, however; from a clinical perspective, it is important that most atypical antipsychotics have also been tested in combination treatments.

Finally, first data are now available on long-term prophylactic efficacy of atypical antipsychotics. These combined efficacy data definitely support the use of atypical antipsychotics in bipolar disorder, and it is now the time to collect more experience with these substances in severely ill patients in clinical settings.

Key words: antipsychotics, aripiprazole, bipolar disorder, clozapine, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone

INTRODUCTION: USEFULNESS AND LIMITATIONS OF TYPICAL ANTIPSYCHOTICS

The primary rationale to test atypical antipsychotics in bipolar disorder was the extensive clinical experience and established usefulness of classical antipsychotics in manic disorder. Due to their rapid sedative and antipsychotic effect these drugs proved to be useful in psychiatric, agitated and hostile patients. Especially in those patients not willing to take medication at all, the availability of intramuscular formulations was helpful. However, their disadvantages are obvious. A significant short-coming is the limited, if at all, efficacy in prophylaxis (Moffors et al, 1981; Esparon et al, 1986). While treating mania with a classical antipsychotic drug, the clinician is afraid of the emergence of depressive symptoms (Harrow et al, 1994). The major disadvantages are the numerous side effects ranging from anticholinergic and cognitive side effects to typical extrapyramidal syndromes (EPS) and, for worst, tardive dyskinesia. In up to 80% of bipolar patients acute EPS have been observed (Brüne, 1999) whereas tardive dyskinesia are described in up to 35% of bipolar patients with long-term neuroleptic treatment (Mukherjee et al, 1986).

Nevertheless, typical antipsychotics are widely used in most parts of the world. In Germany, a census of the "Arzneimittelüberwachung in der Psychiatrie" (AMUP) Bayern, held in 1998, covered 275 acutely manic patients in different Bavarian state hospitals. In this study, an extensive use of typical antipsychotics has been noted. Of all manic patients, 83% received antipsychotics (Grünze and Dobmeier, 2002). In addition to this evidence, of clinical use, some controlled studies also support the efficacy of classical antipsychotics. As of 1999, 9 controlled studies comparing haloperidol to different standards have been published. In most of these, haloperidol was found to either beat the comparators or have at least equal efficacy (Grünze, 1999). None of these trials, however, had a placebo arm. Efficacy of haloperidol against placebo has only been shown recently in one monotherapy study (unpublished data, Astra Zeneca, on file) and one add-on study (Sachs et al, 2002b). Haloperidol, used as a comparator, was superior to placebo in both studies.

Typical antipsychotics appear to be of special usefulness in severely manic and psychotic patients. The Northwick Park study (Johnstone et al, 1988), which compared pimozide, lithium and placebo in 120 patients with functional psychosis found that pimozide was effective both for mania and psychotic symptoms, whereas lithium was effective on elevated mood only. With the broadening of the bipolar spectrum, psychotic symptoms have been accommodated fairly well within the scope of bipolar disorder as long as they do not dominate the clinical picture and overshadow the mood symptoms. Thus, a considerably higher number of patients will be diagnosed as bipolar disorder with psychotic symptoms, demanding treatment that is different from established mood stabilizers such as lithium. Atypical antipsychotics, combining probably the broader effectiveness of classical antipsychotics with improved tolerability may thus be appropriate for this new challenge.

MONOTHERAPY WITH ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DISORDER

Derivatives of clozapine: Olanzapine and quetiapine

Clozapine can be considered as the
father of atypical antipsychotics. Numerous case reports and several small investigator-initiated trials support its antmanic as well as mild antidepressive and good prophylactic efficacy in bipolar patients (Frye et al, 1998). Thus, clozapine may be considered as a true mood stabilizer in contrast to typical antipsychotics; the latter may worsen depressive symptoms and appear not efficacious in prophylactic treatment. However, all these data are derived from small and often poorly controlled investigator-initiated trials. The large-scale methodologically unambiguous studies are missing due to the lack of commercial interest and the potentially life threatening side effects of clozapine.

This situation is clearly different for the new generation of atypical antipsychotics emerging since the beginning of the 1990s. Two of them, olanzapine and quetiapine, show receptor affinities relatively similar to that of clozapine. Like clozapine, their D2 receptor occupancy level is relatively lower than their affinities for histaminergic (H1) receptors, 5-HT2A receptors (for olanzapine) and apha receptors (for quetiapine). Both substances appear to be tolerated very well. Agranulocytosis does not seem to be a problem, however, the clinical experience is still limited.

Olanzapine has shown significant superiority over placebo in two double-blind placebo-controlled monotherapy studies (Tohen et al, 1999; Tohen et al, 2000). These studies had a duration of three and four weeks, respectively, applying a maximum dose of 20 mg/day of olanzapine. It is of interest, that especially in the 4-week study (Tohen et al, 2000) a relatively large number of patients with mixed states (43%) had been included. In both studies, more than 50% of patients showed psychotic features also. It is of clinical importance that the improvement, as measured by the fall in the Young Mania Rating Scale (YMRS) scores, was not different in psychotic and non-psychotic manic patients. Thus, improvement cannot be explained as a function of treatment of psychotic symptoms alone as, obviously, there are genuine effects on mood. No difference in efficacy measures could be found when comparing patients with and without rapid cycling (Tohen et al, 2000). In the same vein, patients with pure mania responded very similar to those with mixed symptomatology. In patients with marked depressive symptoms, there was also a significant improvement of the Hamilton Depressive Rating Scale (HAMD) during olanzapine treatment compared to placebo. Thus, although conducted for purposes of registration with regulatory authorities, these placebo-controlled data furnish clinically important information of a broader spectrum of efficacy for olanzapine.

Every new potential mood stabiliser should not only beat placebo, but also have at least comparable efficacy to clinical standards. Two double-blind placebo-controlled trials compared olanzapine with valproate in acute mania. In the trial of Tohen et al (2002a) olanzapine outperformed valproate on the primary outcome, the reduction of the YMRS after three weeks. However, this study may be criticized on the ground that valproate was likely to be under-dosed; only 87% of the manic patients reached sufficient plasma levels above 50 μg/l. In a second study comparing olanzapine and valproate, Zajecka et al (2000) used higher doses of valproate (mean dose 2115 mg/day compared to 1401 mg/day in the previous study). In this study, no significant difference between groups was found for YMRS reduction, however valproate appeared to have been better tolerated than olanzapine, on the whole. In times of increasing economic pressure, it may be also of note that the twelve week treatment costs for valproate were $541, and for olanzapine $1,080. These two trials are also a typical example that the outcome of trials, even considered as methodologically clean, clearly depends on dosing and other methodological issues (and finally on the sponsor).

For quetiapine, acute monotherapy data have not been published, so far. However, four large scale, placebo-controlled, double blind trials have just been concluded recently; three of these show a significant advantage of quetiapine. One trial had additionally included haloperidol as a comparator arm. The overall outcome after eight weeks was similar for quetiapine and haloperidol. Haloperidol showed a slightly faster onset of action whereas quetiapine was clearly better tolerated by the patients. For a more detailed review of these trials, one has to wait for the data to be published.

Ziprasidone and risperidone

These two atypical antipsychotics define themselves mainly by a very pronounced serotonergic component of action, both having a similar occupancy profile for the 5-HT2A receptor. Ziprasidone has additional occupancy of the 5-HT2A receptor. The dopaminergic D2 receptor affinity is relatively stronger than with clozapine, quetiapine or olanzapine, which may also result in higher incidence of EPS when overdosed. Ziprasidone was tested for antimanic efficacy in a double-blind placebo-controlled multicentre study for the duration of three weeks, including 197 patients. The primary outcome parameter was the Mania Rating Scale, which consists of 10 items from the SRDS-C. Thus, this study had a design that was very similar to the pivotal study by Bowden et al (1994), comparing valproate against lithium and placebo. Ziprasidone was significantly superior to placebo starting from day 2 until day 21, the endpoint of the study (p<0.001). In the PANSS positive subscale, the secondary outcome parameter, ziprasidone also showed a significant effect on psychotic symptoms in these manic patients.

For risperidone, double-blind placebo-controlled monotherapy trials have been conducted but, as with quetiapine, are not published so far. We are aware of two trials and both showed a significant ananstmatic response with risperidone as compared to the placebo arm (Janssen-Cilag, data on file). In one of these studies, conducted in India, a mean reduction of 21 points in the YMRS was observed, an antimanic response hardly ever seen in any controlled Phase III trial. However, approximately 50% of the patients had EPS also. One may argue that in general, the India patients have a lower body weight and that they might have been receiving a much higher dose as compared to US and European trials.

Aripiprazole

The chemical structure and the receptor
occupancy profile of Aripiprazole appear slightly different from other atypical antipsychotics. Aripiprazole is a partial agonist of D₂ and 5-HT₆ receptors. Its receptor binding affinity is high for D₂, D₃, 5-HT₆, 5-HT₇, and moderate for D₁, alpha and H₁, whereas it has no affinity for M₁. Three acute mania studies have been presented in scientific meetings as posters so far. They include two 3-week long studies against placebo and one 12-week long study against haloperidol. Aripiprazole was superior showing clear, significant separation from placebo at day 4 in one study, whereas in the other only a trend to higher efficacy was observed, mainly due to an extraordinary high placebo response rate of 38%. No difference in efficacy was observed in the haloperidol comparator study at endpoint, however, aripiprazole was clearly better tolerated.

THE USEFULNESS OF ATYPICAL ANTIPSYCHOTICS IN COMBINATION TREATMENT

Monotherapy trials are needed to show unambiguous efficacy of a drug, even though combination treatment is the clinical reality. For example, looking prospectively into the treatment of 258 patients of the Stanley Foundation Bipolar Network, it was noted that patients receive an average of 4.1 medications for mood stabilization (Post et al., 2002). This trend towards combination treatment has also been demonstrated in other studies (Frye et al., 2000), indicating our own, conducted in the outpatient clinic in Munich as a part of the Stanley Foundation Bipolar Network (Dittmann et al., 2002). However, until recently only a few controlled trials were designed to test efficacy in combination treatment. Now we have three pivotal trials for olanzapine, risperidone and quetiapine looking into this issue.

In the study of Tohen et al. (2002b) patients were treated with either valproate or lithium for acute mania. Those not showing sufficient response after three weeks were then randomised and treated in a double-blind fashion with either olanzapine (n=230) or placebo (n=114) as an add-on. Olanzapine treated patients had a significant better outcome reflected by the YMRS, total score after six weeks of treatment. Again, a positive effect was also noted on the Hamilton Depression Rating Scale (HAM-D) scores, especially in patients with mixed episodes with moderate or severe depressive symptoms. Concerning the YMRS, as with the placebo-controlled trials, olanzapine outperformed placebo also in patients with mixed mania and psychotic symptoms.

For quetiapine, two studies using an add-on design have been presented recently. In a study by Sachs and colleagues (Sachs et al., 2002a) quetiapine was used as an adjunct treatment to lithium or valproate for 21 days in acutely manic patients. For the primary outcome criteria (YMRS) as well as for several secondary outcome criteria, including the CGI-BP, a significant advantage of quetiapine co-administration was observed. The incidence of adverse events was generally low and discontinuation due to these events was similar in both groups.

The other study by Del Bello et al. (2002) tested the usefulness of quetiapine add-on to valproate compared to placebo add-on for the treatment of acute mania in adolescents. Thirty patients were included in the study, and again the YMRS response rate was significantly greater in the valproate plus quetiapine group than in the valproate plus placebo group (87% versus 53%). Side effects were again scarce and not different from the placebo group. These findings are of special importance as predominant symptoms of mania in adolescents are often psychotic features, mixed states and rapid cycling (Carlson and Kashani, 2002; Findling et al., 2001), and so far few studies looked systematically into response rates and tolerability in younger patients.

Risperidone was also tested in two trials, one conducted in the US and one internationally, for its efficacy in manic or mixed episodes, applying an add-on design to previous mood stabilizer treatment. In the US study (Sachs et al., 2002b) lithium or valproate were allowed as mood stabilizers, whereas in the international study, carbamazepine could also be used. In addition, the US study had a haloperidol arm as an internal comparator. In the US study, both haloperidol and risperidone was statistically significantly superior to the add-on placebo arm. Significance for risperidone was missed in the international study at first analysis. When excluding those patients who had been on carbamazepine, however, the international study was also able to show a significant advantage of risperidone add-on treatment compared to placebo (Yatham, 2000). From this study, it becomes obvious that combination treatment, including those with atypical antipsychotics, has to be conducted good skill keeping in mind the possibility of drug-drug interactions, for example on the level of the cytochrome P450. Both the US and the international study showed comparable efficacy for risperidone in patients exhibiting psychotic features or not. Side effects of risperidone were generally low, especially compared to haloperidol where a significantly higher incidence of EPS was observed.

In general, there seems to be a consensus that the side effects with atypical antipsychotics are lower in comparison to typical antipsychotics. This is an important issue as it may determine patients' compliance. Weight gain is clearly a disadvantage of clozapine and olanzapine and less pronounced in risperidone and quetiapine, whereas ziprasidone is almost weight neutral. Weight gain is also associated with the increased risk of cardiovascular mortality, which is 1.6 times higher in treated bipolar patients and 2.1 times higher in untreated bipolar patients, compared to the general population (Angst et al., 2002). Thus, when choosing the appropriate atypical antipsychotic for treating bipolar patients, this issue should be kept in mind and discussed openly with the patient.

Effects of olanzapine on depressive symptoms in mixed patients have already been described previously for the monotherapy trials. In a recent combination treatment trial, olanzapine was compared against placebo and a combination of olanzapine and fluoxetine for the treatment of psychotic depression (Dubé et al., 2002). In this double-blind 8 week trial, both olanzapine and the combination of olanzapine and fluoxetine separated significantly from placebo response in the Montgomery Asberg Depression Rating Scale.
(MADRS), the primary outcome criterion. However, the time to response was clearly shortened by the combination of olanzapine and fluoxetine compared to both placebo and olanzapine monotherapy. Preliminary data for risperidone (Canuso, 2003) also support an antidepressant component of action.

As suicidality obviously threatens bipolar depressed patients (Bottlender et al, 2000), it is of highly relevant clinically that better and faster acting treatments are developed for depressive episodes in bipolar patients. In this context, it is of interest that a recent study by Meltzer and colleagues (Meltzer et al, 2003) demonstrated antisuicidal effects of clozapine in schizophrenic and schizoaffective patients.

MAINTENANCE TREATMENT: FIRST EXPERIENCES WITH ATYPICAL ANTIPSYCHOTICS

Data on long-term efficacy of atypical antipsychotics in bipolar patients are still very limited. In a six month open study, 541 patients received risperidone as an add-on treatment to previous mood stabiliser treatment (Viesta et al, 2001). Both the mean YMRS and HAMD scores declined rapidly and remained on a low level in these bipolar I, bipolar II, or schizoaffective patients. For olanzapine, three controlled studies, one against placebo and two against comparators (valproate and lithium) furnish first evidence for a long-term prophylactic effect.

In the placebo controlled study (Tohen, 2002), patients in acute manic or mixed episodes of bipolar I disorder were treated with open-labelled olanzapine for a period of 6-12 weeks. Those achieving symptomatic remission (YMRS <=12 and HAMD-21 <=8) were randomized to olanzapine (N=225) (5-20 mg/d) or placebo (N=136) for another 52 weeks of double-blind treatment. Whereas 80.1% of patients randomized to placebo suffered from at least one new episode during the following year, only 46.7% of patients on olanzapine relapsed (p<0.001). Extending on the previously cited acute mania trial comparing olanzapine and valproate, Tohen et al (2001) conducted a 47 week continuation, double-blind parallel group trial in those patients who responded to either valproate or olanzapine in acute mania. There was no significant difference in the number of manic relapses or in the median time to relapse between olanzapine and valproate treatments, however, there was a tendency to have fewer fresh manic episodes with olanzapine.

The prophylactic antimanic efficacy of olanzapine is also supported by a recently presented 12 months double blind trial comparing olanzapine and lithium in patients who were euthymic at the beginning of the study (Tohen et al, 2002c). Olanzapine outperformed lithium both in the survival analysis and in the percentage of patients who relapsed into mania. No difference was observed with respect to the percentage of patients who experienced a depressive relapse. Thus, olanzapine may constitute an alternative to lithium in prophylactic treatment for patients who have predominantly manic episodes. If preventing new depressed episodes is of similar clinical importance, combination therapies, e.g. with lamotrigine, should be considered (Goodwin et al, 2002).

CONCLUSIONS

Atypical antipsychotics are an emerging treatment for bipolar patients as summarized in the Table 1. Both controlled and real world studies with risperidone, olanzapine, ziprasidone, quetiapine and aripiprazole showed efficacy in treating acute mania. Atypical antipsychotics seem also to improve depressive symptoms or at least do not worsen depression as conventional antipsychotics may do. Controlled data, though preliminary in nature, also support prophylactic efficacy especially for olanzapine.

| Substance       | Euphoric mania | Mixed mania | Bipolar depression | Rapid cycling | Maintenance in general | Prophylaxis of Euphoric mania | Prophylaxis of mixed mania | Prophylaxis of Bipolar depression | Prophylaxis of Rapid cycling |
|-----------------|----------------|-------------|--------------------|---------------|------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Ziprasidone     | +++            | +++         | 0                  | 0             | 0                      | 0                             | 0                             | 0                             | 0                             |
| Risperidone     | +++            | ++          | +                  | +             | +                      | +                             | +                             | +                             | +                             |
| Quetiapine      | ++             | +           | +                  | ++            | +                      | ++                            | +                             | +                             | +                             |
| Olanzapin       | +++            | +++         | +                  | +++           | ++                     | +++                           | +                             | +                             | +                             |
| Clozapine       | +              | +           | +                  | +             | +                      | +                             | +                             | +                             | +                             |
| Ziprasidone     | +++            | +++         | 0                  | 0             | 0                      | 0                             | 0                             | 0                             | 0                             |

+++ Efficacy in double-blind, controlled studies, published in peer-reviewed journal
++ Efficacy in double-blind, controlled studies data published as abstract and presented on conferences
+ Efficacy in open studies, no double-blind controlled studies published so far
0 To the authors knowledge, no studies in bipolar disorder conducted so far
and partially also for risperidone. For olanzapine, the suppression of manic episodes seems to be the more pronounced mode of action. However, we definitely need more controlled data, especially placebo-controlled data, for all atypical antipsychotics with regard to long-term efficacy and prophylactic treatment. A main advantage of atypical antipsychotics is their relatively good tolerability, at least compared to conventional antipsychotics. This is definitely a key issue for long-term compliance of patients. Besides studying long-term efficacy of atypical antipsychotics in controlled studies, it is now also of importance to have more large-scale naturalistic studies in clinical populations of bipolar patients. Comorbidity in bipolar patients is the rule, rather than exception. Atypical presentations are at least as common as classical clinical pictures. Thus, large-scale simple trials with atypical antipsychotics will broaden our knowledge about the real-world clinical effectiveness of this class of agents and also give us more information about long-term safety of these novel compounds.

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