Eur Arch Psychiatry Clin Neurosci (2005) 255 : 83–93 DOI 10.1007/s00406-005-0580-z

REVIEW

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Antidepressive effects of traditional and second generation antipsychotics: a review of the clinical data

Received: 10 January 2005 / Accepted: 9 February 2005

Abstract For a long time, in the context of depressive symptoms in schizophrenia traditional neuroleptics were mostly discussed with respect to possible depressiogenic side effects, although some studies argued that they may also have certain antidepressive effects. However, this was not proven at that time in placebo-controlled studies. Placebo-controlled studies performed in recent years have shown that second generation antipsychotics have antidepressive effects which are significantly stronger than those of the traditional neuroleptics. In addition, it was demonstrated that this antidepressive effect can only partially be explained as being secondary to the improvement of positive and negative symptoms, and is apparently predominantly due to a direct (primary) effect on depressive symptoms. It is of special relevance in this context that the antidepressive effect of second generation antipsychotics was recently demonstrated in depression. The positive results from some studies in bipolar depression are especially impressive and underline the antidepressive potencies of novel antipsychotics beyond the spectrum of schizophrenia.

Key words second generation antipsychotics · antidepressive efficacy · schizophrenia · depression

Introduction

Depressive symptoms during schizophrenic psychoses represent an important part of the overall spectrum of psychopathological symptoms, not only in the schizoaffective types but also in the core groups of schizophrenic psychoses diagnosed according to ICD-10 or DSM-IV (Bottlender et al. 2000; Häfner et al. 1999; Wassink et al. 1999). The clinical relevance of these symptoms stems from the patients' suffering and the association with suicidality, as well as from the necessity to treat depressive symptoms in the context of schizophrenia.

Although the traditional neuroleptics, beside the risk of inducing depressive symptoms, seem to have a certain antidepressive effect, the second generation antipsychotics are apparently superior in their antidepressive potency (Möller 2000 a). The second generation antipsychotics therefore appear to represent a new option for the treatment of depressive symptoms in schizophrenic patients. This seems to be of special importance given the fact that the efficiency of treatment with antidepressants is limited, and furthermore, particularly when SSRIs are used, there is a risk of pharmacokinetic interactions (Möller 2004; Siris and Bench 2003; Whitehead et al. 2002).

The expectations concerning an antidepressive effect of novel neuroleptics are based on theoretical deliberations. These are derived from the pharmacological mechanisms of the novel neuroleptics, which differ from those of the classical neuroleptics (Möller 2005). The clinical data available so far on antidepressive effects of novel antipsychotics in schizophrenia are still limited and have been obtained almost exclusively from ex post analyses of Phase III studies which were primarily aimed at proving antipsychotic efficacy.

It is the aim of this paper to describe the current level of clinical knowledge on antidepressive effects of traditional or second generation antipsychotics in schizophrenic patients. It is of particular interest to analyse whether the novel antipsychotics are superior to traditional neuroleptics in this respect. Finally, it should be examined whether neuroleptics have direct effects on the depressive mood or "only" work indirectly via effects on positive and negative symptoms and thereby only affect these concomitant (secondary) depressive symptoms. In face of the limited database about antidepres-

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sive effects of novel antipsychotics in the frame of schizophrenic psychoses, findings from studies of novel antipsychotics in the treatment of depression will also be considered to round off the topic.

This review is based on a systematic screening of publications in Medline as well as on respective information from the abstract books of recent international congresses. In addition, pharmaceutical companies were approached and asked to provide information.

Effects of traditional neuroleptics on depressive mood in schizophrenic patients

The traditional neuroleptics were not systematically evaluated with respect to a possible antidepressive effect in the context of schizophrenic psychoses. Furthermore, for a long time the hypothesis of a depressiogenic effect of traditional neuroleptics was in the foreground of the clinical discussion, including concepts such as 'pharmacogenic depression', 'neuroleptic-induced dysphoria', 'akinetic depression' and 'postpsychotic depression' (Helmchen and Hippius 1967; McGlashan and Carpenter 1976; Rifkin et al. 1975; Siris and Bench 2003; Van Putten and May 1978).

Although such relationships could be demonstrated, it was not possible, for example, to attribute all depressions present after easing off of the acute psychosis to the neuroleptic treatment alone (Möller et al. 1985; Möller and von Zerssen 1982, 1986). Overall the picture of depressive symptoms during schizophrenia, the possible causal factors and differential diagnosis is very complex. However, the possibility that depression may be caused by traditional neuroleptics, at least in a subgroup of patients, should still be seen as a clinically relevant problem (Awad 1993; Browne et al. 1998; Siris and Bench 2003). This assumption is also supported by the studies mentioned above as well as by some studies from the early phases of neuroleptic treatment (e. g. De Alarcon and Carney 1969; Floru et al. 1975; Galdi et al. 1981; Galdi 1983; Johnson 1981). Two studies from the 1990 s also deliver further indications in this direction: A large prospective study found that patients who were maintained on neuroleptic medication manifested more depression than those who were randomized to receive neuroleptic medication only on an 'early intervention' or 'crisis intervention' basis, and patients in that study were found to have lower depression ratings after being taken off neuroleptic medication (Bandelow et al. 1992). Another well-designed study specifically comparing anhedonia in schizophrenic patients on versus off neuroleptics found significantly more anhedonia as well as more depression in those patients who were being treated with neuroleptics (Harrow et al. 1994). At least one study found a positive relationship between haloperidol plasma levels and depressive symptoms in the context of a positive association between extrapyramidal and depressive symptoms (Krakowski et al. 1997), and another study found a trend level association between the degree of depression and neuroleptic dose (Perenyi et al. 1998).

Without denying a depressiogenic effect of the traditional neuroleptics seen in a subgroup of schizophrenic patients, in general traditional neuroleptics have a certain antidepressive effect, at least in acute schizophrenic patients, apparently resolving depressive symptoms that accompany positive symptoms (Knights and Hirsch 1981; Möller et al. 1985; Möller and von Zerssen 1982, 1986). Unfortunately this antidepressive efficacy was not very well evaluated, especially not in a placebo-controlled manner, until the time that traditional neuroleptics such as haloperidol were used as the standard comparator in clinical trials on novel neuroleptics. Thus most of the earlier evidence was obtained from naturalistic studies. Although the placebo-controlled comparator studies from the past decade were able to confirm some antidepressive effect, they also demonstrated that second generation antipsychotics are superior in this respect (see next section).

Furthermore, in this context it is relevant to mention the tradition of combining antidepressants with traditional neuroleptics in the treatment of schizodepressive syndromes and delusional depression. In this way it was possible to achieve not only a reduction of psychotic symptoms but often also the clinical impression of a better global antidepressive response (Möller 1990; Spiker et al. 1985).

While it is widely reported that traditional neuroleptics may cause depressive symptoms during schizophrenic disorders (see above), the second generation antipsychotics appear to have no such risk. Furthermore, several findings show that these substances seem to be more effective than the classical neuroleptics in reducing depressive symptoms occurring during schizophrenia (Möller 2000a, 2000 b). This is apparently related to their different pharmacological properties (Möller 2005).

Antidepressive effects of second generation antipsychotics in schizophrenic patients

Results on antidepressive effects of second generation antipsychotics were mostly obtained from ex post analyses of data from phase III studies that were primarily performed to prove antipsychotic efficacy in patients suffering from an acute schizophrenic episode. They therefore only allow limited conclusions to be drawn about efficacy in treating depressive symptoms of schizophrenic patients. Not all of the results were positive, and the antidepressive effect was not always statistically significant, often because the studies did not have enough statistical power to answer this question. A depression scale in the stricter sense, such as the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS), was used in several of these studies; in some others, only a depression-related subscore of a schizophrenia scale

such as the Brief Psychiatric Rating Scale (BPRS) or the Postive and Negative Syndrome Scale (PANSS) was calculated. In all respective studies the sample was not enriched for schizophrenic patients suffering from depressive symptoms; however, in some studies the analysis was performed on a subgroup of patients reaching a certain cut-off score for depressive symptoms. Some of the findings were only presented in the context of pooled analyses of several studies of the respective drugs, without publishing the results of each single trial. Given all these methodological limitations, further studies are therefore required, especially with the primary objective to evaluate the antidepressive efficacy of second generation antipsychotics in the context of schizophrenic psychoses in a confirmative manner. The antidepressive effects of the novel antipsychotics should be demonstrated more often not only versus placebo but also compared to a traditional standard neuroleptic such as haloperidol.

Several of the controlled studies that investigated antidepressive effects of second generation antipsychotics were hitherto only presented at congresses and have not yet been published as full papers. Thus the following review cannot be seen as fully comprehensive.

In three double-blind studies on schizophrenic patients comparing olanzapine with haloperidol, olanzapine showed better efficacy in treating depressive symptoms compared to placebo and haloperidol, measured with the MADRS (Tollefson et al. 1997, 1998a, 1998 b). Based on a reanalysis of the data from the so-called North American risperidone study, Marder et al. demonstrated a better antidepressive effect of risperidone compared to placebo and haloperidol using a PANSS-derived anxiety/depression cluster (Marder et al. 1997). Peuskens et al. (2000) analysed the effect of risperidone, in comparison to haloperidol and placebo, on depressive symptoms by combining the results of six double-blind studies on schizophrenic patients. In a PANSS-derived anxious/depressive cluster, patients of the risperidone group showed more marked improvement of depressive symptoms than those who received haloperidol or placebo. Stronger effects than haloperidol on depressive symptoms of schizophrenic patients have also been described for amisulpride (Muller et al. 2002; Peuskens et al. 2002) and quetiapine (Emsley et al. 2003).

Ziprasidone and aripiprazole were introduced to the market in recent years, whereby aripriprazole was licensed most recently. In a double-blind study on 139 patients with an acute exacerbation of their schizophrenia or schizoaffective disorder, which compared 40 versus 120 mg/day ziprasidone with placebo (Keck et al. 1998), 120 mg/day ziprasidone was significantly more effective than placebo in reducing the derived anxious-depressive subscore of the BPRS; ziprasidone 40 mg/day did not show a significant antidepressive effect. Similar results were obtained from a study on acute schizophrenic patients comparing 80 versus 160 mg/day ziprasidone with placebo; in this study only the 160 mg/day dosage achieved a statistically significant difference to placebo (Daniel et al. 1999). In a 28-week study in stabilised, schizophrenic patients, 80–160 mg/day ziprasidone was superior to haloperidol 5–15 mg/day in terms of MADRS score reduction (Hirsch et al. 2002). Regarding the antidepressive effects of aripiprazole on schizophrenic patients, hitherto only the data from a pooled analysis of two 52-week extension studies comparing aripiprazole with haloperidol have been published (Kasper et al. 2003). The primary aim of these studies was to demonstrate maintenance of antipsychotic efficacy. Aripiprazole was able to demonstrate stronger effects in reducing a PANSS-derived depression/anxiety cluster.

It is of interest that, as far as head-to-head comparisons between different second generation antipsychotics have been performed and subanalyses of the antidepressive effects calculated, differences have mostly not been found (Conley and Mahmoud 2001; Peuskens et al. 2002; Simpson et al. 2004). A risperidone-olanzapine comparative study (Conley and Mahmoud 2001) demonstrated a slight advantage for risperidone. It is of special interest that despite its special pharmacological profile with noradrenalin- and serotonin-reuptake inhibition properties, which are comparable to those of imipramine (Schmidt et al. 2001), so far ziprasidone has not demonstrated stronger antidepressive effects than olanzapine (Simpson et al. 2004). The same is true for zotepine, which, in addition to the pharmacological mechanisms related to its antipsychotic effects, has relatively strong effects on noradrenalin reuptake.

To give an impression of the strength of the antidepressive effect, the results of a review of four head-to-head comparisons of amisulpride versus haloperidol, flupenthixol and risperidone (Rein et al. 1998) are summarised in Fig. 1. It is of interest that in the two comparative studies versus haloperidol, the antidepressive effect of amisulpride was significantly superior. This was also the case for the comparison with another traditional neuroleptic, flupenthixol, which was classified in the older literature as having a stronger impact on mood than other traditional neuroleptics. Only compared to risperidone was there no difference: both antipsychotics reduced depressive symptoms in the context of schizophrenia to the same degree.

In order to give a more detailed impression of the antidepressive effects of second generation antipsychotics, the results of one study will be described in more detail. The study by Tollefson et al. (1998 b) is quite interesting under methodological aspects as it included several subanalyses. In this 17-country, double-blind, comparative investigation, 1996 patients with schizophrenia or a related diagnosis were randomly assigned (2:1 randomisation) to olanzapine (5–20 mg/d) or haloperidol (5–20 mg/d). The average dose during the initial phase of the study was 13 ± 15 mg olanzapine or 12 ± 10 mg haloperidol. In order to estimate the frequency of at least moderate depressive signs and symptoms, the sample was stratified a priori by a baseline MADRS score of 16 or higher. According to this a priori criterion, 1047

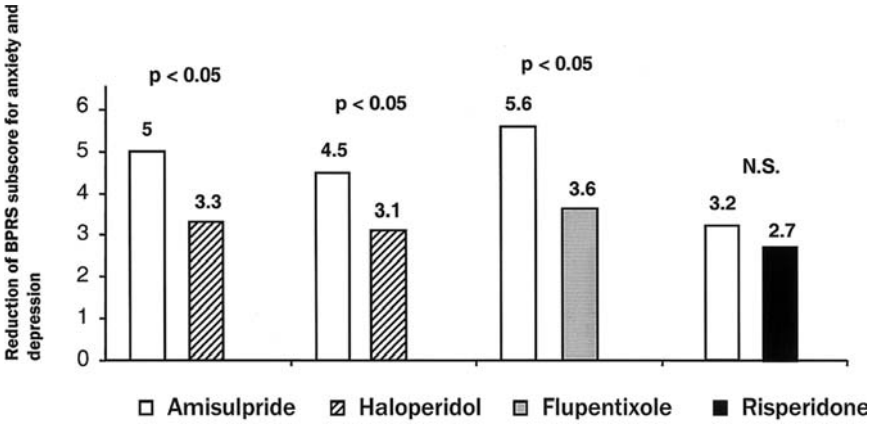

Fig. 1 Significant improvement of affective symptoms during treatment with atypical neuroleptics; results of studies with amisulpride. Review by Rein et al. (1998) which summarised the data from the following studies: Möller et al. (1997), Puech et al. (1998), Wetzel et al. (1998), Peuskens et al. (1999)

persons, or 53 % of the overall sample, were at least moderately depressed (olanzapine treatment group: 694; haloperidol treatment group: 353). A secondary definition, requiring only a MADRS item 1 (apparent sadness) mood score of 2 or higher, yielded a similar prevalence estimate. Another a priori secondary definition, a cluster of six BPRS 'depression' items (somatic concern, anxiety, guilt feelings, depression, tension and motor retardation), defined moderate depressive signs and symptoms as a cluster score of 10 or higher. This definition characterised 61 % of the total sample. All these rates underscore the clinically relevant prevalence of depressive symptoms in patients suffering from an acute episode of schizophrenia.

Both neuroleptics demonstrated an improvement (Fig. 2) in the 6-week study by baseline-to-endpoint change on the MADRS (LOCF). Olanzapine, however, exhibited a significantly greater treatment effect ($p = 0001$) among all patients. The total group of olanzapine-treated patients ($n = 1053$) experienced a mean ($\pm$ SD) change of -5.97 ± 8.69 in the MADRS total scores versus -3.06 ± 8.78 points for the total group of haloperidol-treated patients ($n = 428$). Within the MADRS total score change, item 1 (apparent sadness) improvement was also more prominent in the olanzapine than in the haloperidol group ($p < 0.001$). All 10 MADRS items demonstrated greater improvement with the use of olanzapine than with haloperidol. The BPRS 6-item depression cluster showed a baseline-to-endpoint change that also significantly favoured the use of olanzapine ($p = 0.02$). Among the individual six BPRS cluster items, scores for both the depression and motor retardation items demonstrated significantly greater improvement with the use of olanzapine than with haloperidol ($p = 0.01$; $p = 0.03$, respectively). A more stringent definition of response, i. e., 50 % or greater improvement from the baseline MADRS total score (on those patients completing at least 3 weeks of the treatment), demonstrated a significantly higher response rate among olanzapine-treated (46 %) than haloperidol-treated (35 %) patients ($p = 0.001$). Weekly BPRS depression cluster scores (observed case) were analysed (Fig. 3). The difference between the two treatments significantly favoured the use of olanzapine beginning at week 1 ($p = 0.03$) and throughout the remainder of the initial 6-week phase.

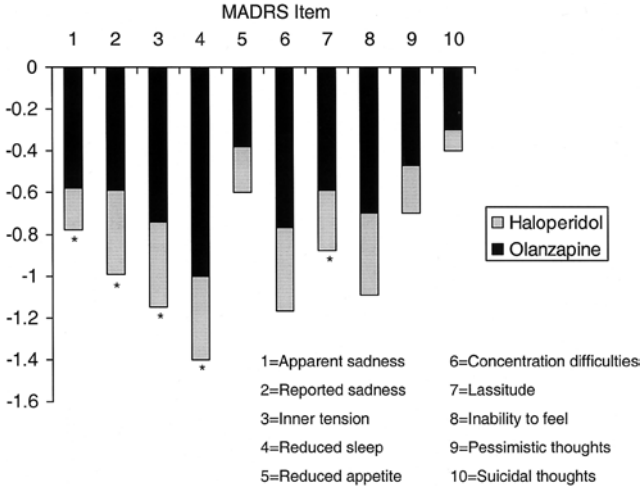

Fig. 2 The individual Montgomery-Asberg Depression Rating Scale (MADRS) item contributions to the total score change. Those with an asterisk represent significant between-treatment differences (items 1–4 and 7), which all favoured olanzapine. The grey bar represents haloperidol-associated change, whereas the sum of both the grey and black bars represent olanzapine-associated changes (Tollefson et al. 1998 b). * $p < 0.05$

When the same analyses were conducted on the MADRS score stratum of 16 or higher at baseline, the MADRS between-treatment effects were magnified to a mean ($\pm$ SD) score of -9.69 ± 9.02 for olanzapine-treated patients ($n = 538$) vs. -5.66 ± 8.96 for haloperidol-treated patients ($n = 229$). This treatment-effect difference significantly favoured the olanzapine-treated patients ($p = 0.001$) and was about twice as large as that seen among the haloperidol-treated patients. Overall there was a strong and positive correlation between initial 6-week change scores in the LOCF MADRS total and the following rating scales: BPRS total, BPRS depression cluster, PANSS, positive PANSS and negative subscales. Among patients with a predominant negative or mixed negative symptoms presentation (Kay et al. 1986) ($n = 913$), the change in the MADRS scores with the use of olanzapine (-6.4 ± 8.9) was significantly

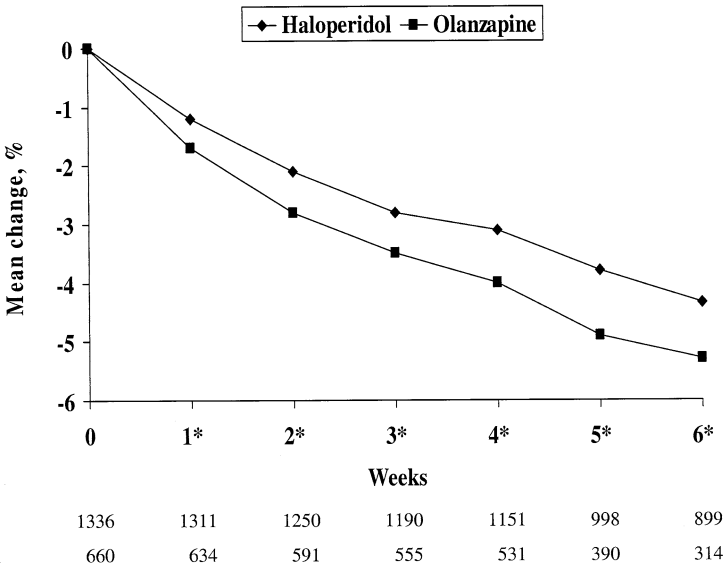

Fig. 3 A plot of weekly (observed case) change between treatments on the Brief Psychiatric Rating Scale depression cluster scores. Weekly change, beginning at Week 1, favoured olanzapine during the 6-week phase of the study (Tollefson et al. 1998 b). * $p < 0.05$

greater ($p = 0.005$) than that seen with haloperidol (-3.4 ± 9.0). The magnitude of the change in the MADRS scores was less among patients with predominantly positive symptoms but still significantly favoured the use of olanzapine (olanzapine treatment group, -5.8 ± 8.1; haloperidol treatment group, -2.6 ± 7.9; $P = 0.005$) (Tollefson et al. 1998 b).

At least for theoretical considerations it is interesting to investigate the question whether the antidepressive effects of the new antipsychotics are 'only' secondary effects via reduction of positive symptoms and the accompanying negative symptoms – or whether these are direct effects on depressive symptoms. In order to differentiate between primary and secondary effects, the path analytical approach was applied, which has already been shown to differentiate between direct and indirect effects of neuroleptics on negative symptoms (Möller et al. 1995). Using this approach it was possible to demonstrate that the difference between the treatment effects of olanzapine and haloperidol on depressive symptoms can only be explained to a certain degree by the effects on positive symptoms and especially on negative symptoms and extrapyramidal side effects, and that therefore a fairly substantial amount is independent of such treatment differences, i. e. can be interpreted as a direct effect on depressive symptoms (Tollefson et al. 1998a, 1998 b) (Fig. 4). A similar result was also found for quetiapine in comparison to haloperidol (Emsley et al. 2003). However, if the placebo comparisons are considered, the proportions are different. A path-analytic comparison of olanzapine (15 mg/day) versus placebo revealed secondary contributions from both the positive (51 %) and negative (28 %) symptom advantages of olanzapine. Approximately 21 % of the olanzapine treat-

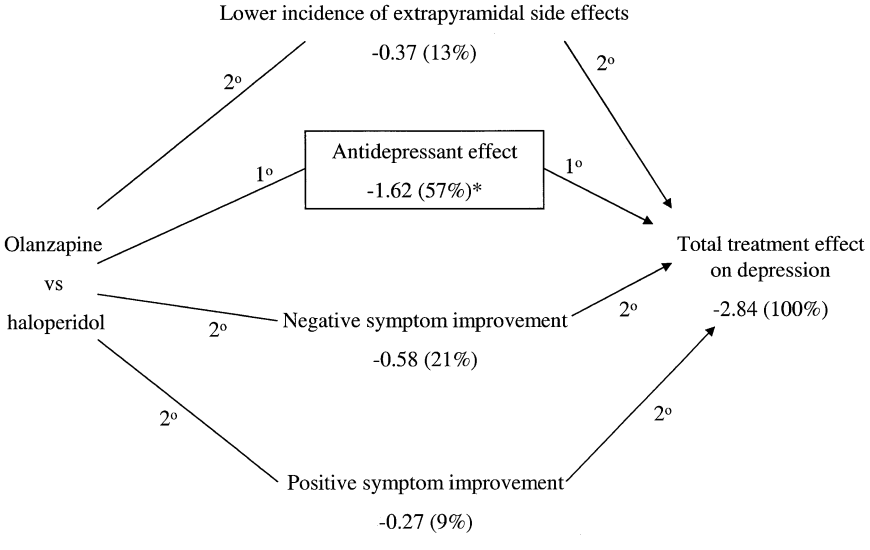

Fig. 4 Exhibit of the 'path-analytic' model illustrating the relationships between positive, negative, extrapyramidal and mood symptoms and their relative contributions to Montgomery-Asberg Depression Rating Scale score changes. The majority and a significant change is attributable to a primary or 'direct' effect on mood (Tollefson et al. 1998 b). * $p < 0.001$

ment advantage on depression/anxiety was a direct treatment effect (Tollefson et al. 1998 a).

To date there are no substantial indications that second generation antipsychotics cause depression, as has been shown for typical neuroleptics, at least in a subgroup of schizophrenic patients. Due to their special pharmacological mechanisms of effect (Möller 2005), the new antipsychotics probably do not block the dopaminergic reward system to such a degree as is characteristic for the traditional neuroleptics. Furthermore, the additional pharmacological mechanisms outside the dopaminergic system counteract a depressive effect caused by D_2 blockade.

The favourable profile of effect of the new antipsychotics with respect to depressive symptoms in schizophrenic patients may also be of relevance for suicidality. It is well known from several studies that suicidality is a relevant clinical problem in the course of schizophrenic psychoses (Siris 2001). There are also numerous indications for an association between depression and suicidality in schizophrenic disorders (Bottlender et al. 2000). It can be expected that the quality of effect of the atypical neuroleptics in that, unlike the traditional neuroleptics they do not cause pharmacogenic depression, and perhaps even reduce depressive symptoms occurring during schizophrenia, will result in a reduction of suicidality as part of schizophrenic disorders. A mirror design study on clozapine presented interesting results in this direction in that it showed not only a lower frequency of suicidality after switching from the neuroleptic pre-treatment to clozapine but also a reduction in the depression and hopelessness scores (Meltzer and Okayli 1995). The hopelessness score is seen by suicidologists as being the most relevant predictor of suicidal behaviour. Recently the efficacy of clozapine in reducing suicidality was demonstrated in a prospective study versus olanzapine (Meltzer et al. 2003), in which clozapine was superior to olanzapine.

Evidence for the antidepressive efficacy of second generation antipsychotics from studies in depression

There is strong support for the antidepressive effects of second generation antipsychotics from studies in the field of depression. Especially recently performed controlled studies are of great relevance in this context.

The combination of an antidepressant with a neuroleptic is already known from the era of traditional neuroleptics to be an effective treatment approach (Spiker et al. 1985). This strategy has been further investigated and gained additional support since the advent of the second generation antipsychotics (Rothschild 2003). Casuistic reports and retrospective studies in the field of major depression with psychotic symptoms give some indications of efficacy of second generation antipsychotics (Adli et al. 1999; Banov et al. 1994; Chacko et al. 1993; Dassa et al. 1993; Hillert et al. 1992; Jacobsen 1995; Keck Jr. et al. 1995; Naber et al. 1992; Nelson et al. 2001; Parsa et al. 1991; Ranjan and Meltzer 1996; Rothschild et al. 1999; Sajatovic et al. 1991; Wood and Rubinstein 1990; Zarate Jr. et al. 2000).

Of special interest are the results of randomised, controlled studies in this indication. In their comparison of risperidone with a combination of haloperidol and amitriptyline in patients suffering from a combined psychotic and depressive syndrome in the frame of schizophrenia, schizoaffective disorder or delusional depression, Müller-Siecheneder et al. (1998) found the combination of the typical neuroleptic haloperidol with an antidepressant to be statistically significantly superior to the monotherapy with the atypical antipsychotic risperidone. This could be interpreted as a disadvantage of treatment with risperidone alone in terms of depressive symptoms. Under methodological aspects the best studies in major depression with psychotic features are two studies on olanzapine (Rothschild et al. 2004). The purpose of these studies was to compare the efficacy and safety of olanzapine (OLZ) monotherapy and an olanzapine/fluoxetine combination (OFC) with placebo (PLA) for unipolar major depression with psychotic features. Under a single protocol, two 8-week, double-blind trials were conducted at 27 sites. Patients (n = 124 trial 1, n = 125 trial 2) were randomised to 1 of 3 treatment groups: OLZ (5 to 20 mg/d), PLA, or OFC (olanzapine 5 to 20 mg/d + fluoxetine 20 to 80 mg/d). The primary outcome measure was the 24-item Hamilton Depression Rating Scale total score. For trial 1, endpoint improvement for the OLZ group (–14.9) was not significantly different from the PLA or OFC groups. The OFC group had significantly greater endpoint improvement (–20.9) than the PLA group (–10.4, P = 0.001); this significant difference was present within 7 days of therapy and maintained at every subsequent visit. The OFC group also had significantly higher response rate (63.6 %) than the PLA (28 %, P = 0.004) or OLZ (34.9 %, P = 0.027) groups. For trial 2, there were no significant differences among treatment groups on the 24-item Hamilton Depression Rating Scale total scores or response rates.

Of interest in this context are also some randomised controlled studies with small doses of amisulpride (e. g. 50 mg/day) in the indication dysthymia. In two double-blind, placebo-controlled studies, amisulpride appeared to be equivalent to amineptine (Boyer et al. 1999) and to imipramine (Lecrubier et al. 1997); in an open-label study it showed similar efficacy to paroxetine (Rocca et al. 2002). Similarly, indications of antidepressive efficacy of small doses of amisulpride were found in major depression in two double-blind, parallel-group studies: Cassano et al. (2002) suggested equivalence for amisulpride compared to paroxetine, and Amore et al. (2001) for amisulpride compared to sertraline.

Hints about antidepressive efficacy of second generation antipsychotics have been provided by case records and open-label studies on refractory depression. In most of these studies, the antipsychotic was administered as an add-on treatment to an ongoing

therapy with SSRIs (Dimova 2003; Dunner et al. 2003; Hirose and Ashby Jr. 2002; O'Connor and Silver 1998; Ostroff and Nelson 1999; Papakostas et al. 2004; Parker and Malhi 2001; Rapaport et al. 2003; Schar et al. 1995; Stoll and Haura 2000; Thase 2002; Vavrusova 2002). However, this has to be further investigated in methodologically more sound studies.

The results of an 8-week, double-blind controlled study in patients with refractory unipolar depression comparing olanzapine, fluoxetine and the combination of both are also of importance (Shelton et al. 2001). Although the sample size was very small (n = 28), the efficacy data are interesting. Fluoxetine monotherapy produced minimal improvement on various scales that rate severity of depression. The benefits of olanzapine monotherapy were modest. Olanzapine plus fluoxetine produced significantly greater improvement than either monotherapy on one measure and significantly greater improvement than olanzapine monotherapy on the other measures after 1 week. Unfortunately the monotherapy effects of fluoxetine or olanzapine were not placebo controlled. Thus only the data for the combined therapy can be interpreted as hints of efficacy, compared with the results of each monotherapy, in refractory unipolar depression. It is notable that the therapeutic response in the olanzapine group was more or less of the same low level as in the fluoxetine group. However, this should not be interpreted as an indication of equipotent antidepressive efficacy, given the limited effect and the small sample size. Olanzapine might have advantages in this special sample due to the treatment refractory state of the patients (refractory to antidepressants, not to neuroleptics!). The impressive antidepressive effect of the combination might be explainable by a special impact of this drug combination. Using microdialysis it was demonstrated in rats that the combination of fluoxetine and olanzapine increases the release of both noradrenalin and dopamine in addition to the reuptake inhibition induced by fluoxetine (Zhang et al. 2000).

Another study that evaluated the olanzapine-fluoxetine combination (OFC) versus olanzapine (OLZ), fluoxetine (FLX) and nortriptyline (NTP) in monotherapy has hitherto only been published in abstract form (Dube et al. 2002a). The 8-week, double-blind study was performed in 499 patients with treatment-resistant depression (defined as historic SSRI failure and failure of a 7-week nortriptyline lead-in phase). OFC subjects demonstrated significantly better total scores on the MADRS than the monotherapies from week 1 to 4, except OLZ at week 3. OFC maintained the treatment effect throughout the 8 weeks; however, at endpoint it was only statistically separated from OLZ (–8.6, –6.5). Sub-analysis of subjects with more than 3 depressive episodes within the last two years also demonstrated the fast OFC onset of action, and statistical separation from OLZ and FLX at endpoint (–11.33, –4.57, –5.76). Subjects with SSRI failure during the current major depressive episode demonstrated fast OFC onset of action, and statistical separation from component monotherapies through week 7, and from OLZ at endpoint (–9.66, –5.16). OFC's safety profile was similar to component monotherapies. The authors concluded that OFC had a rapid onset of action and was particularly efficacious in subsets of more treatment-resistant subjects.

The results of the above mentioned 8-week study on treatment-resistant depression were combined with those of a similarly designed 12-week study in this special group of patients (n = 797) in a meta-analytic evaluation, the results of which are only available as a congress abstract (Dube et al. 2002b). OFC patients achieved significantly greater total score improvement at week 1 (–7.31) than olanzapine (–5.18, $p = 0.013$) or fluoxetine (–5.26, $p = 0.004$) patients and maintained the significant effect throughout 8 weeks of treatment (11.60; –7.55, $p < 0.001$; –8.73, $p < 0.001$). OFC patients had a significantly greater endpoint response rate than olanzapine (37.3 %, 21.1 %) patients and significantly greater endpoint remission rates than olanzapine or fluoxetine (24.9 %, 13.1 %, 15.2 %). The authors concluded that OFC showed rapid improvement in depressive symptoms by week 1 of treatment and sustained treatment effect throughout 8 weeks of therapy. The combination demonstrated significant advantage over either monotherapy, and represents a promising treatment for patients with treatment-resistant depression.

Additional proof of an antidepressive efficacy of new antipsychotics has been obtained from two studies on acute bipolar depression. First, the results of the olanzapine study will be presented. A total of 833 randomised patients with bipolar I depression were investigated in a double-blind, 8-week, randomised controlled trial (Tohen et al. 2003). The main inclusion criterion was an MADRS score of at least 20. Patients were randomly assigned to receive placebo (n = 377), olanzapine, 5 to 20 mg/d (n = 370), or olanzapine-fluoxetine combination, 6 and 25, 6 and 50, or 12 and 50 mg/d (n = 86). The main outcome measures were changes in MADRS total scores using mixed-effects model repeated measures analyses (MMRM). The mean modal drug dose for the olanzapine monotherapy group was 9.7 mg/d. The mean drug dose for the combination group was 7.4 mg/d for olanzapine and 39.3 mg/d for fluoxetine. The percentage of patients who used benzodiazepines at least once during the study was not statistically significantly different between groups (placebo group: 43.5 %; olanzapine group: 43 %; olanzapine-fluoxetine group: 36 %). The MMRM analyses of visit-wise mean changes in MADRS scores are depicted in Fig. 5. There were significant main effects for treatment ($p < 0.001$) and for visit ($p < 0.001$), with no significant treatment x visit interaction ($p = 0.43$). As to between-group comparisons for visit-wise MADRS mean change, starting as early as week 1 and continuing throughout the study, the olanzapine and olanzapine-fluoxetine groups demonstrated significantly greater mean improvements in MADRS total scores than those receiving placebo. Starting at week 4 and continuing to

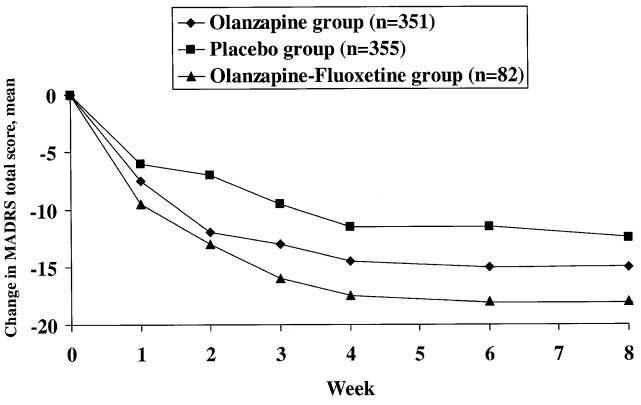

Fig. 5 Least squares mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total scores during the 8-week study. Improvement in MADRS scores with use of olanzapine and the olanzapine-fluoxetine combination was significantly greater than with use of placebo throughout the study ($p < 0.001$). Improvement in MADRS scores with use of olanzapine-fluoxetine combination was significantly greater than with use of olanzapine at weeks 4 to 8 ($p < 0.02$) (Tohen et al. 2003)

week 8, the olanzapine-floxetine group also demonstrated significantly greater mean improvement in MADRS total scores than the olanzapine monotherapy group. The therapeutic effect sizes for olanzapine and olanzapine-fluoxetine were 0.32 and 0.68, respectively. The response rate for the olanzapine group was 39 %, which was significantly higher than the rate for the placebo group of 30.4 % ($p = 0.02$). The response rate for the olanzapine-fluoxetine group was 56.1 %, which was significantly higher than that for the placebo ($p < 0.001$) and for the olanzapine ($p = 0.006$) groups. Median times to response for the placebo, olanzapine and olanzapine-fluoxetine groups were 59, 55 and 21 days, respectively. Time to response was significantly shorter for the olanzapine group compared with the placebo group ($p = 0.01$) and shorter still for the olanzapine-fluoxetine group compared with the placebo ($p < 0.001$) and olanzapine ($p = 0.005$) groups. The remission rate for the olanzapine group was 32.8 %, which was significantly higher than the rate for the placebo group of 24.5 % ($p = 0.02$). The remission rate for the olanzapine-fluoxetine group was 48.8 %, which was significantly higher than that for the placebo ($p < 0.001$) and olanzapine ($p = 0.007$) groups. Median estimated times to remission for the placebo, olanzapine and combination groups were 59, 57 and 42 days, respectively. Time to remission was significantly shorter for the olanzapine group compared with the placebo group. Of great interest are the analyses of individual MADRS items. The olanzapine and olanzapine-fluoxetine groups showed statistically significant improvements on inner tension, reduced sleep and reduced appetite compared with the placebo group but apparently not in the core items of depression. In addition to the items mentioned above, the olanzapine-fluoxetine group showed statistically significant improvement on core mood items, including apparent sadness, reported sadness, lassitude, inability to feel and pessimistic thoughts, compared with the olanzapine and placebo groups (Tohen et al. 2003).

The results of the above study show that the antidepressive effects of olanzapine are significantly superior to those of placebo, although apparently it does not tackle the core items of depression. The antidepressive effect of the combination of olanzapine with fluoxetine was significantly superior to that of monotherapy with olanzapine alone and included core items of depression. These results may indicate that the antidepressive effect of olanzapine alone in the treatment of acute bipolar depression does not reach a ceiling effect, and can be increased by combining olanzapine with fluoxetine. This could also lead to the question whether monotherapy with olanzapine is of similar efficacy as with fluoxetine. However, for an exact interpretation of the results in this respect a treatment arm that received fluoxetine monotherapy would be required, which was unfortunately lacking in this study. Principally it might not be permissible to extrapolate from the add-on effects of fluoxetine to the monotherapy effects of fluoxetine. However, the results of the single-item analysis could be interpreted as a hint that olanzapine alone might not be able to influence the core items of depression.

In an analogue 8-week, randomised, double-blind clinical study a fixed dose of either 300 mg/day or 600 mg/day quetiapine was compared to placebo in 542 patients with bipolar I and II disorders. The main results of the study were presented by Calabrese et al. as an abstract at the APA Congress 2004 (Calabrese et al. 2004). Patients taking quetiapine achieved a significantly greater improvement ($p < 0.001$) in mean MADRS and Hamilton Rating Scale for Depression (HAM-D) scores versus placebo at every time point starting at week 1 through to week 8. Significantly more patients taking quetiapine ($p < 0.001$) were considered to be responders (> 50 % decrease from baseline MADRS score) from week 2 through to the end of the study. After 8 weeks, significantly more patients taking quetiapine achieved remission from their depressive symptoms compared to the placebo group (53 % vs. 28 %, respectively, $p < 0.001$), as evaluated on the MADRS scale. The effect sizes in this study were 0.8 for 600 mg/day quetiapine versus placebo and 0.66 for 300 mg/day quetiapine versus placebo. As this study lacked an antidepressant control arm, the question whether the antidepressive efficacy of quetiapine is on a comparable level to that of antidepressants still remains open and requires further investigation.

To our knowledge there is no published meta-analysis of the antidepressive effects of second generation antipsychotics in schizophrenic patients or in both schizophrenic and depressive patients.

Conclusions

All together there is a fair amount of evidence from placebo-controlled studies that second generation antipsychotics have an effect on depressive symptoms in

schizophrenia. In addition, there is evidence that second generation antipsychotics have a better effect on depressive symptoms in schizophrenia than traditional neuroleptics. The antidepressive effect is apparently to a certain degree independent of effects on positive and negative symptoms. Although there are some limitations in the methodology of these trials – especially the fact that the results were obtained from secondary or ex post analyses of studies designed primarily to demonstrate antipsychotic efficacy – the consistency of these results is convincing.

The antidepressive properties of second generation antipsychotics are additionally supported by confirmative studies from the field of depression. These adequately designed studies demonstrated efficacy in psychotic depression, refractory unipolar depression and acute bipolar depression.

The data available so far seem to justify the conclusion that second generation antipsychotics should be preferred to traditional ones, firstly to avoid pharmacogenic depression and secondly to treat depressive symptoms of schizophrenia.

Based on the limited amount of data on antidepressants in the comorbid condition of acute schizophrenia and a depressive syndrome (Levinson et al. 1999; Whitehead et al. 2002), it can be assumed that comorbid depression can generally be sufficiently treated with second generation antipsychotics and that in most cases there might be no need for coadministration of antidepressants.

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