Drug Treatment of Depressive Symptoms in Schizophrenia

Hans-Jürgen Möller [1]

Abstract

Depressive symptoms during schizophrenic psychosis represent an important part of the overall spectrum of psychopathological symptoms, not only in the schizoaffective type but also in the core groups of schizophrenic psychosis diagnosed according to the *International Classification of Diseases-10 (ICD-10)* or the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)*. Their clinical relevance stems from the patients' suffering and the association with suicide, as well as from the necessity to treat depressive symptoms in the context of schizophrenia. Besides the potential risk of inducing depressive symptoms, the first-generation antipsychotics seem to have a certain antidepressive effect, in the sense that depressive symptoms secondary to positive symptoms can be alleviated with the reduction of positive symptoms. The second-generation antipsychotics seem to have no risk to induce depressive symptoms, appear to have better antidepressive effects and, therefore, represent a better option for the treatment of depressive symptoms in schizophrenic patients. However, the evidence for this is based predominantly on ex post analyses of data from Phase III trials, and the results are not consistent. Administration of antidepressants in combination with antipsychotics seems to be a meaningful option to treat depressive symptoms in schizophrenia. However, data collected hitherto show that treatment with antidepressants in addition to neuroleptic treatment is only of limited benefit. This might especially be the case in combining antidepressants with second-generation antipsychotics. The risk of inducing positive symptoms by antidepressants has to be considered, although the evidence is limited in this respect. Furthermore, there is a risk of pharmacokinetic interactions, particularly with selective serotonin reuptake inhibitors (SSRIs).

Key Words: Depression in Schizophrenia, Antipsychotics, Antidepressants

The Prevalence, Classification and Clinical Relevance of Depressive Symptoms in Schizophrenia

Depressive symptoms can be observed in all stages of schizophrenia, i.e., in the prodromal phase, the acute episode, the postpsychotic stage and over the long-term course (1-6).

[1]*Department of Psychiatry, University of Munich*

Address for correspondence: Prof. Hans-Jürgen Möller, Department of Psychiatry, University of Munich, Nussbaumstrasse 7, 80336 Munich, Germany
Phone: +49 89 5160 5501; Fax: +49 89 5160 5522;
E-mail: hans-juergen.moeller@med.uni-muenchen.de

Submitted: July 3, 2007; Revised: September 17, 2007; Accepted: September 19, 2007

Data differ on the prevalence of depressive symptoms during the course of schizophrenic psychoses. They depend on whether it is a cross-sectional or longitudinal study, and on the diagnostic system and rating scales applied (7). Prevalences ranging from 7 to 65% have been determined (8, 9). In their long-term catamnesis (clinical approach without using standardized rating scales), Gross and Huber (10) described depressive symptoms at various time points during the course of the illness in 12% of the patients with schizophrenia (broad clinical diagnosis including schizoaffective psychosis). The prevalence of depressive symptoms appears to be higher in more recent studies, which may be due to the use of standardized assessment procedures. In their 4.5- to 7.5-year follow-up study, Sands and Harrow (11) detected depression in 30 to 40% of the patients. In patients with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders–III (DSM-III)*, Martin and colleagues (12) determined a lifelong prevalence of 65% for *DSM-III* major depression.

Depressive symptoms traditionally have been viewed as predictors for a positive prognosis in the short- and long-term of schizophrenia; however, in the recent past this has been questioned (13, 14). From a clinical perspective, depressive symptoms are of great importance for several reasons. Besides the personal suffering of the patients, and especially the impact on daily functioning, the risk of suicidal ideas and suicidal behavior has to be considered (15, 16). Thus the burden of depressive symptoms for schizophrenic patients (17) should be noted very carefully by clinicians. The right choice of drug treatment, together with supportive therapy, can lead to a more positive outcome, not only concerning the risk of suicidal behavior (18), but also in general.

Depressive symptoms can be observed in the acute phase of schizophrenia and usually lessen during remission, even under treatment with first-generation antipsychotics (FGAs) (8, 19-26). Some authors, based on epidemiological and follow-up research, conclude that there might be a specific relationship between affective symptoms and schizophrenic positive symptoms (5, 6). Knights and Hirsch (19) coined the term "revealed depression" to characterize the unveiling of previously existent depressive symptoms after reduction of the positive symptoms. Other authors described postpsychotic depression as a heterogeneous group caused by different etiological factors (25, 27-29).

While in earlier literature both depressive symptoms and other symptoms, e.g., from the psychopathological spectrum of anxiety and compulsive symptoms, were seen as a symptomatological part of the complex psychopathological phenomenology of schizophrenic psychoses, no additional conclusions were usually drawn, particularly not with respect to etiopathogenetics. The modern approach of a depressive comorbidity appears to be more indicated, i.e., it does not only mean coexisting symptoms or syndromes, but apparently the coexistence of two illness entities (morbus = illness).

The *ICD-10* especially addresses the coexistence of schizophrenia and depression in two categories: the postschizophrenic depression (PSD) and the schizoaffective disorder, depressive type. Of course, this is only a limited approach because there are other types of depression in the context of schizophrenia than just postschizophrenic depression and schizodepressive disorder. The *DSM-IV* diagnostic criteria for depression in schizophrenia, still among the Criteria Sets and Axes Provided for Further Study, use the term postpsychotic depressive disorder of schizophrenia (PDDS). Both criteria sets (the *ICD-10* and the *DSM-IV*) for postpsychotic depression are based on the criteria for depressive episodes with some modifications, and include an item to avoid the diagnosis of a depressive episode during the acute psychotic episode. The *DSM-IV* criteria include an item to exclude depressive symptoms that are better accounted for as medication side effects or negative symptoms. The main incompatibility between the two criteria is the fact that the *ICD-10* PSD criteria limit the diagnosis of depressive episode to the twelve months following the psychotic episode, while the *DSM-IV* PDDS criteria do not have time limitations (30).

Schizoaffective psychosis is a special model example of the close interlocking of two disorder groups. It was traditionally not only conceptualized as a cosyndrome or comorbidity, but also seen as the result of an etiopathogenetic amalgamation process between schizophrenic and affective disorders, which may be supported, at least partially, by family genetics and other etiopathogenetic findings. The mere description in terms of cosyndromality or comorbidity would not fully describe this concept. The repeatedly discussed unitary psychosis ("Einheitspsychose"), which fully combines the schizophrenic and affective psychosis as belonging to the same disease with a common etiopathogenetic background, can be seen as the extreme of this conceptualization (31-34). Angst (35) performed a very comprehensive review of the historical aspects of the dichotomy between schizophrenia and affective disorders.

Besides etiopathogenetic implications, a comorbidity approach may possibly also have other compelling therapeutic consequences in the sense that comedication approaches then appear to become more indicated - according to the motto: every illness must be treated - than if the coexistence of symptoms from different disease groups is interpreted as cosyndromality in the sense of the multifariousness of the psychopathological expression of an illness. Such a pure cosyndrome approach does not always mean that an antidepressant has to be administered in addition to an antipsychotic in order to treat adequately the whole spectrum of the schizophrenic disorder of a certain patient. For example, there is a large number of data showing that depressive symptoms/depression scores of patients suffering from an acute schizophrenic episode are reduced during drug treatment with first-generation antipsychotics in the context of the reduction of positive symptoms. This is even more the case with modern antipsychotics (SGAs) (36).

While the modern comorbidity approach, which contrasts with the more restrictive meaning of the term "morbus," is to be understood only in the sense that not only one syndromatically defined disorder is present according to the *ICD-10* or *DSM-IV* criteria, but at least two disorders are present. This approach, by definition, already clarifies the severity of the cosyndromal symptoms with respect to number, intensity and, if necessary, duration. The traditional cosyndromality approach initially does not make such a differentiation, but records every cosyndrome purely descriptively in order to then differentiate in a further step according to the severity of these symptoms. As a result, the cosyndro-

mality approach does not primarily define any threshold values above which comedication may make sense or is even required. These threshold values have to be determined in a secondary step, e.g., by definition of various degrees of intensity of the cosyndromatic symptoms by means of a dimensional scale.

Depressive symptoms in schizophrenic patients have to be clinically differentiated from antipsychotic-related side effects (29) such as neuroleptic-induced dysphoria, neuroleptic- induced akathisia and, especially, neuroleptic-induced akinesia (37, 38). Akinesia syndrome can closely mimic either the negative syndrome (39) or depression in schizophrenia such as postpsychotic depression (40), especially from negative symptoms. For example, anhedonia, reduced interest, anergia and limited capacity for concentration might overlap (41, 42). The differentiation from negative symptoms, based on the different symptomatic pictures, can be sometimes difficult, even for experienced clinicians (43).

Rating scales for the assessment of depression, like the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS) can help to determine the severity of depression, while others, for instance, the Scale for the Assessment of Negative Symptoms (SANS) or the Positive and Negative Syndrome Scale (PANSS) do the same for negative symptoms. However, there is a symptomatic overlap, which gives a certain score on the depression scale, although the patients suffer only from negative symptoms and vice versa. The application of the Calgary Depression Scale (44), which tried to eliminate this overlap as much as possible, offers certain advantages (45).

To summarize, 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* (1, 2, 46). The clinical relevance of these symptoms stems from the patients' suffering and the impact on functioning, as well as the association with suicide. Due to the burden of depressive symptoms for schizophrenic patients, it is necessary to treat depressive symptoms in the context of schizophrenia.

A crucial point is the question of when a special medication or comedication for depressive symptoms should be introduced, i.e., only in cases with a full depressive episode according to *ICD-10* or *DSM-IV*, or also in subthreshold conditions, or at a certain depression score. Besides all categorical or dimensional criteria, in the end the suffering of the individual patient will guide the physician in his/her decision.

Antidepressive Effects of Second-Generation Antipsychotics

Early after their clinical introduction, the first-generation antipsychotics (FGAs) were described as having a risk of inducing depressive symptoms in schizophrenic patients, especially the higher potent D2-blockers like haloperidol (47, 48). This was called in the German literature "pharmacogenetic depressive," while in the United States publications the term "akinetic depressive" (37) was coined to underline the relationship between parkinsonian side effects (akinesia) and depressive mood. According to clinical experience, the reduction of the dose of the antipsychotic can be a meaningful approach to the reduction of those depressive effects. Apart from this, the administration of anticholinergics seems to be beneficial (49).

However, despite the risk of inducing depressive symptoms in the context of schizophrenia, there is the expectation that depressive symptoms can be alleviated with the reduction of positive symptoms (49-51). Still, the effects at that early stage of the clinical psychopharmacology of antipsychotics almost exclusively were described in naturalistic studies, not in randomized, controlled group studies (see Figure 1) (50, 52, 53).

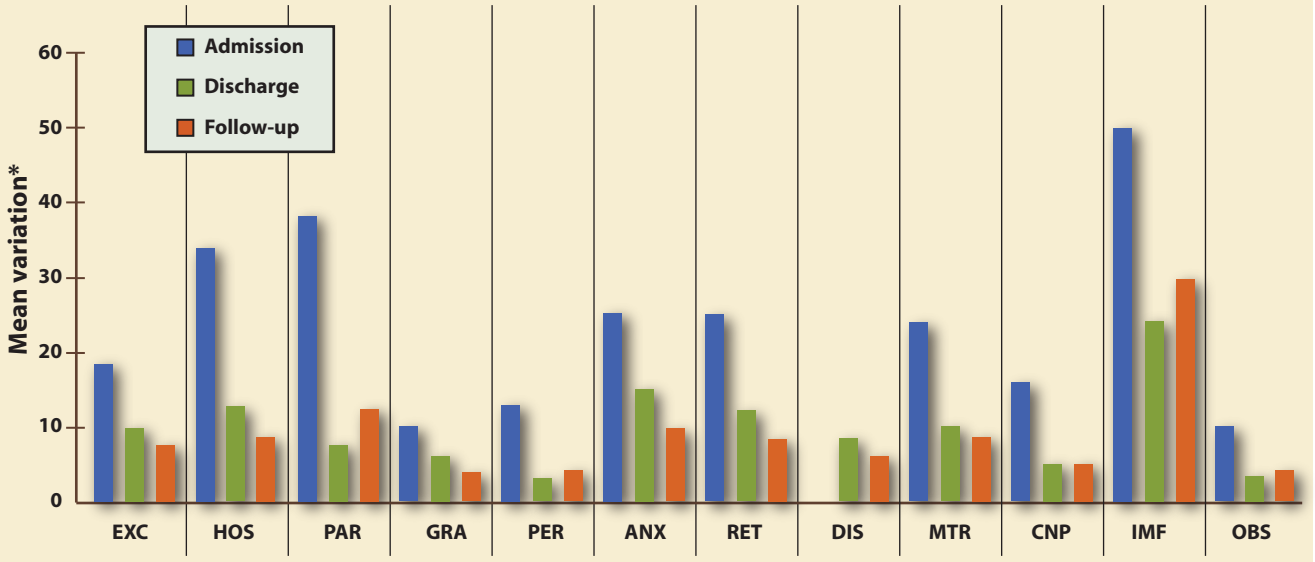
Second-generation antipsychotics are apparently superior in their antidepressive potency (54) and seem to have no, or at least lower risk of inducing depression. The second-generation antipsychotics (SGAs), therefore, appear to represent a new option for the treatment of depressive symptoms in schizophrenic patients.

The positive expectations concerning the antidepressive effect of SGAs are based on theoretical deliberations, which are derived from the pharmacological mechanisms of the SGAs, differing from those of the FGAs (36). Amongst others, a strong 5HT2A antagonism in particular, which is represented in most of the SGAs, should be mentioned. There are other mechanisms relevant for atypical antipsychotics, as well (55).

The clinical data available so far on the antidepressive effects of SGAs in schizophrenia, however, are still limited and have been obtained almost exclusively from ex post analyses of Phase III studies, which were performed by pharmaceutical companies and primarily aimed at proving antipsychotic efficacy for the licensing of the drug.

An element of this other methodological limitation has to be addressed. A depression scale in the stricter sense, such as the HAM-D or the MADRS, was used only in some studies; while in others, only a depression-related subscore of a schizophrenia scale such as the Brief Psychiatric Rating Scale (BPRS) or the PANSS was calculated. In all respective studies the sample was not enriched for schizophrenic patients suffering from depressive symptoms; however, in

Figure 1 **Inpatient Multidimensional Psychiatric Scale (IMPS) Factor Scores**



*Mean variation as a percentage of the maximum value (49)
EXC=Excitement; HOS=Hostile Belligerence; PAR=Paranoid Projection; GRA=Grandiosity; PER=Ideas of Persecution; ANX=Anxious Depression; RET=Retardation; DIS=Disorientation; MTR=Motor Retardation; CNP=Conceptual Disorganization; IMF=Impaired Functioning; OBS=Obsessive.

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 presented only in the context of pooled analyses of several studies of the respective drugs, without publishing the results of each single trial. In this context it should be mentioned that the single studies mostly were powered only for the primary outcome, the total BPRS or PANSS score, not for a secondary outcome criteria, the depressive score. As far as active comparator studies are concerned, the criticism that some of the advantageous results of SGAs in terms of not only better extrapyramidal symptoms (EPS) tolerability, but also in terms of other benefits, might be due to inadequate dosing of the FGA comparator in some studies, has to be considered (56, 57). Given all these methodological limitations only limited conclusions can be drawn concerning the efficacy of SGAs in treating depressive symptoms of schizophrenic patients. Further, carefully designed studies are required, especially with the primary objective to evaluate the antidepressive efficacy of SGAs in the context of schizophrenic psychoses in a confirmative manner. The antidepressive effects of the SGAs should be demonstrated more often not only versus placebo, but also compared to FGAs such as haloperidol.

Several of the controlled studies that investigated the 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 as measured with the MADRS (58-60).

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 (61). Peuskens et al. (62) analyzed 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 in 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 (63, 64) and quetiapine (65).

Ziprasidone and aripiprazole were introduced to the market in recent years; aripiprazole 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 (66), 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 (67). In a twenty-eight-week study in stabilized schizophrenic patients, 80–160 mg/day ziprasidone was superior to haloperidol 5–15 mg/day in terms of MADRS score reduction (68). Regarding the antidepressive effects of aripiprazole on schizophrenic patients, hitherto only the data from a pooled analysis of two fifty-two-week extension studies comparing aripiprazole with haloperidol have been published (69). 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 and subanalyses of the antidepressive effects calculated, differences mostly have not been found (64, 70-73). A risperidone-olanzapine comparative study (70) 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 (74), so far ziprasidone has not demonstrated stronger antidepressive effects than olanzapine (71). 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.

At least for theoretical considerations it is interesting to investigate the question of whether the antidepressive effects of the 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 antipsychotics on negative symptoms (75). Using this approach it was possible, for example, 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. Therefore, a fairly substantial amount is independent of such treatment differences, i.e., can be interpreted as a direct effect on depressive symptoms (59, 60). A similar result was also found for quetiapine in comparison to haloperidol (65).

To date there are no substantial indications that second-generation antipsychotics (SGAs) cause depression. Due to their special pharmacological mechanisms (36), the SGAs probably do not block the dopaminergic reward system to such a degree as is characteristic for the FGAs. Furthermore, other pharmacological mechanisms outside the dopaminergic system like 5HT2A blockade counteract a depressive effect caused by D2 blockade. Finally, the SGAs have a lower risk profile concerning parkinsonian side effects and, thus, a lower risk to induce akinetic depression.

To summarize, there is a fair amount of evidence from placebo-controlled studies that second-generation antipsychotics have efficacy in depressive symptoms in schizophrenia. In addition, there is some evidence that second-generation antipsychotics have a better effect on depressive symptoms in schizophrenia than first-generation antipsychotics. However, this effect is not so strong that it can be found in data from all the studies, insofar as the respective studies are not as conclusive and consistent as the results concerning the better extrapyramidal tolerability of SGAs. The antidepressive effect is apparently, to a certain degree, independent of effects on positive and negative symptoms. Although there are several 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 somewhat convincing. Nevertheless, prospectively designed studies, where the primary objective is to investigate the antidepressive properties of SGAs in schizophrenic patients in comparison to placebo, and standard comparator from the group of SGAs, are deficient.

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, especially, acute bipolar depression (54). The most conclusive data so far, in this respect, have been presented for two quetiapine trials in bipolar depression (76, 77).

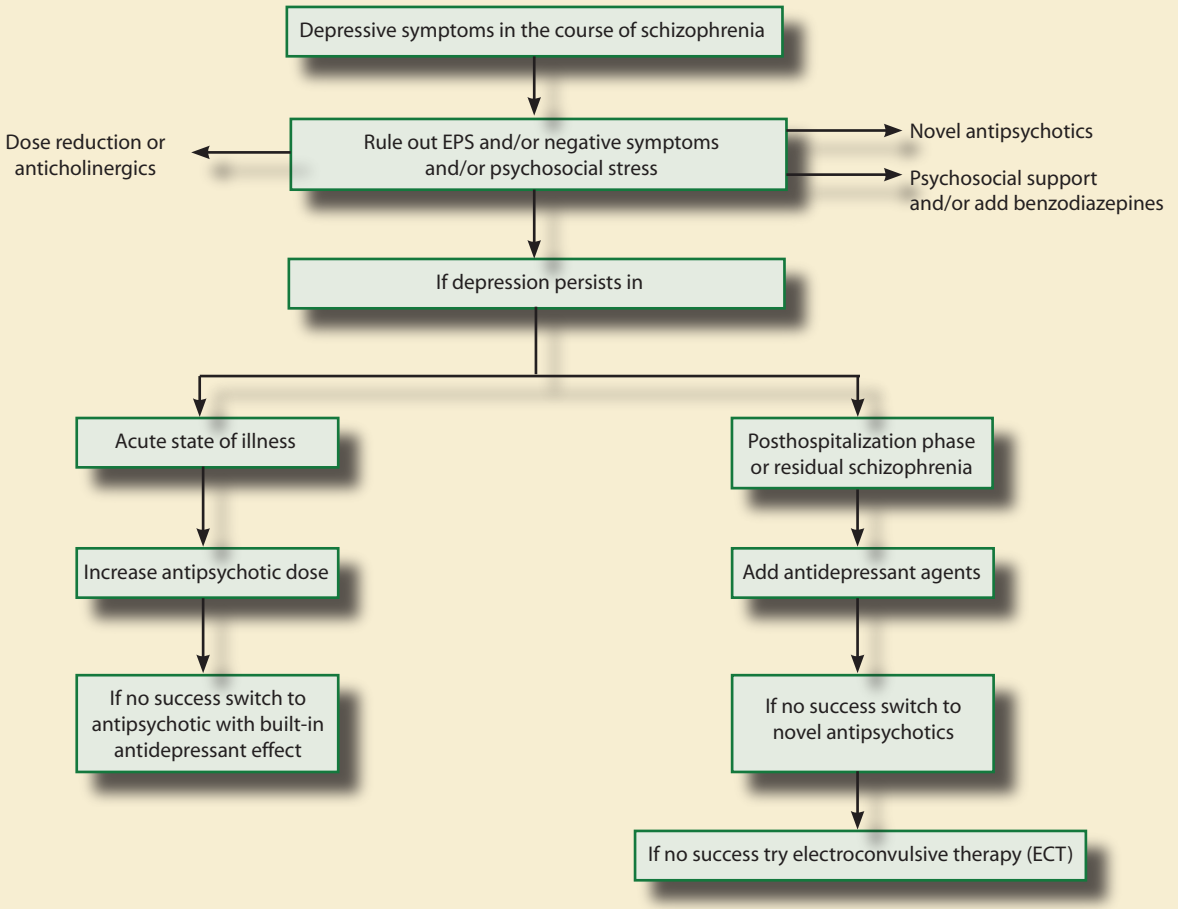
The data available so far seem to justify the conclusion that second-generation antipsychotics should be preferred to FGAs, firstly to avoid pharmacogenic/akinetic depression and, secondly, to treat depressive symptoms of schizophrenia.

Antidepressants as Treatment for Depressive Symptoms in Schizophrenia

For many years, antidepressants have been recommended to treat more severe depressive symptoms during schizophrenic episodes (49), whereby fulfillment of the criteria for comorbidity in the sense of the *ICD-10* or *DSM-IV* criteria was not normally required. Efficacy studies on this subject (78) applied either categorical criteria such as *DSM-IV* criteria for major depression or dimensional criteria such as criteria scored from the HAM-D.

The early literature on this subject indicates that the

Figure 2 **Algorithm for the Proposed Management of Depression in Patients with Schizophrenia (7)**



administration of antidepressants to schizophrenic patients is not unproblematic, and that antidepressants can provoke psychotic symptoms or agitation (79-81). It has, therefore, repeatedly been recommended generally not to give antidepressants to schizophrenic patients without the "protection" of antipsychotics, even if the patients are currently suffering from a purely depressive episode without current schizophrenic symptoms. The dangers of pharmacokinetic interactions (82-85), particularly between modern antidepressants of the selective serotonin reuptake inhibitor (SSRI) type and antipsychotics, must also be kept in mind (86, 87). Pharmacodynamic interactions must also be considered; for example, the cumulative sedative effects are particularly apparent when tricyclic antidepressants are administered (88) or the induction of extrapyramidal side effects, particularly with the SSRIs. The indication for an antidepressant treatment's individual risk-benefit ratio, and the choice of antidepressant to treat depressive symptoms in a schizophrenic patient, should be carefully thought through, considering all of these aspects. The algorithm (see Figure 2) described by Hausmann and Fleischhacker (7) may be useful to determine the indication, although it can be questioned in certain situations and might not give a conclusive answer.

Although there is a long clinical tradition of treating depressive symptoms in schizophrenia, and most clinicians are convinced by their own experience that this is a meaningful approach, one should generally be aware that only limited evidence is available for the efficacy of antidepressants in treating the depressive symptoms of schizophrenia (89). Only a small number of randomized, controlled trials (RCTs) are available in which the efficacy of antidepressants in treating depressive symptoms in schizophrenic disorders was investigated with positive results. Overall, the data are inconsistent and, if positive results are described, some of the effects are not very pronounced.

Most of these studies are add-on studies in which an antidepressant was given to an ongoing neuroleptic medication. Several methodological problems of the studies have to be taken into consideration. Some of them might help to explain why there is such a high rate of negative studies (89). In this respect, the most problematic point is the small sample size of the RCT (n=17 to 60), which leads to a high risk of nondetecting differences (Beta error problem in the statistical sense!). Additionally, other factors might lead to the consequence of not being assigned; e.g., confounders like negative symptoms, parkinsonian side effects, comedication

with anticholinergics, acute versus subchronic psychoses, type and dose of antipsychotics, duration and stability of pretreatment with antipsychotics, and diagnostic aspects such as type of severity of depressive symptoms, etc. Most of the studies are not satisfying in at least several points, and it is difficult to compare these studies due to the lack of standardization concerning these points.

Many of the respective results were obtained from open clinical studies. Kennedy and Miller (90) evaluated 137 schizophrenic inpatients who received amitriptyline in addition to perphenazine and found a remission rate of 86%. Rada and Donlon (91) observed that the administration of low-dose tricyclics quickly alleviated depressive symptoms in schizophrenic patients who did not respond to the phenothiazine-neuroleptic alone. Other authors achieved similarly good results with antidepressants in combination with neuroleptics (89, 92-97).

Only some of the studies applied a randomized, controlled group design (89). A non-placebo controlled RCT compared sertraline 50 mg/day versus imipramine 150 mg/day as an add-on to previous antipsychotic medication; a certain advantage in terms of speed of onset of the antidepressive effects was found for sertraline. In their review from 2003, Siris and Bench (89) reported thirteen randomized, placebo-controlled studies on the efficacy of antidepressants as comedication to antipsychotics (in all SGA studies in schizophrenic patients suffering from a depressive syndrome). Most of the antidepressants used in these studies were tricyclics; in two studies, an SSRI (sertraline) was applied. Most of the placebo-controlled studies showed negative results (8, 81, 88, 98-102). Only the studies by Prusoff et al. (80) and Siris et al. (40, 103), Cooper et al. (104) and Vlokh et al. (105) delivered positive indications. Prusoff et al. (80) showed in a randomized, placebo-controlled trial on schizophrenic outpatients with depressive symptoms that the addition of amitriptyline to perphenazine was more effective in reducing depressive symptoms than neuroleptic monotherapy. Siris et al. (40) in their randomized, placebo-controlled add-on study on schizophrenic patients suffering postpsychotic depression found a better outcome of the imipramine/fluphenazine group compared to the fluphenazine group in both global rating and a specific depression scale. Imipramine was used in a dose between 150-200 mg/day. The same research group examined twenty-four schizophrenic or schizoaffective patients with postpsychotic depression or negative symptoms. All these patients had benefited over the short term by the addition of adjunctive imipramine hydrochloride to their ongoing fluphenazine decanoate/benztropine mesylate regimens, and this adjunctive treatment had been successfully continued for six months. In a randomized, double-blind protocol, treatment with adjunctive imipramine hydrochloride was then either maintained or tapered to placebo for an ensuing one-year trial, while treatment with fluphenazine and benztropine continued. Significantly, more patients who received placebo substitution were also more likely to experience relapses into psychosis.

There is a lack of placebo-controlled studies on SSRIs in the treatment of depression in schizophrenic patients (106). Most of the studies with SSRIs in this indication investigated their efficacy in the treatment of negative symptoms (86). In this context some of these studies also evaluated efficacy in the treatment of depressive symptoms with the interesting result that the changes in negative symptoms mostly did not correlate with changes in the depressive symptoms. For example, Goff et al. (107) published the results of a placebo-controlled study with fluoxetine for the additional treatment of negative symptoms. After a two-week introductory phase with placebo, forty-one schizophrenic or schizoaffective depressive inpatients received 20 mg/day fluoxetine or placebo in addition to a depot conventional neuroleptic in a six-week, randomized, double-blind study. All of the patients had received a stable dose of a depot neuroleptic for at least six months and did not fulfill the criteria for depression. At week six there was a significantly greater reduction of negative symptoms on the BPRS subscale for negative symptoms in patients receiving fluoxetine. None of the other scales showed a significant difference between the two groups, although the values on the depression subscale of the BPRS at week six were 26% lower than at baseline in the patients who received fluoxetine, compared to a reduction of 4% in the placebo group. The improvement of negative symptoms did not correlate with changes in the depressive or extrapyramidal symptoms.

A limiting factor concerning the evidence for the efficacy of antidepressants in depressed schizophrenic patients in general is that most studies on comedication with antidepressants were performed in patients treated with FGAs. It is questionable whether benefits shown under these conditions might not be confirmed in patients treated with atypical neuroleptics, given their better antidepressive effect. Large prospective controlled studies on treating depression in schizophrenia involving the combination of an antidepressant with an SGA have not yet been published. Nevertheless, clinicians in the field seem to be utilizing such combinations for many years already (108), but a conclusive assessment is not yet available.

Cooper et al. (104) investigated schizophrenic outpatients with depressive symptoms on stable ongoing antipsychotic medication. Sertraline was added up to 100 mg daily versus placebo. The outcome in the comedication group was superior to the continuation of ongoing therapy, both in global ratings, as well as on the Beck Depression Inventory.

Vlokh et al. (105) reported positive findings concerning

the add-on treatment with sertraline to an ongoing treatment with antipsychotics. However, the study report does not give sufficient detail, including the lack of a statistical analysis.

The Cochrane metaanalysis (109) reaches a rather critical overall evaluation of the efficacy of antidepressants in the treatment of a depressive syndrome in schizophrenia. Altogether only eleven studies were judged to have sufficiently good methodology to be included; the sample size of most of the studies was no more than thirty patients per arm. For the outcome of "no important clinical response," antidepressants were significantly better than placebo (n=209, five RCTs, summary risk difference fixed effects -0.26, 95% confidence interval [CI] -0.39 to -0.13). The depression score at the end of the trial, as assessed by the HAM-D, seemed to suggest that using antidepressants was beneficial, but this was only statistically significant when a fixed effects model was used (n=261, six RCTs, weighted mean difference [WMD] fixed effects -2.2, 95% CI -3.8 to -0.6; WMD random effects -2.1, 95% CI -5.04 to 0.84). There was no evidence that antidepressant treatment led to a deterioration of psychotic symptoms in the included trials. The final conclusion of the authors is: "At present, there is no convincing evidence to support or refute the use of antidepressants in treating depression in people with schizophrenia. We need further well-designed, conducted and reported research to determine the best approach towards treating depression in people with schizophrenia" (109).

To summarize, the results of randomized, controlled studies of the add-on treatment with antidepressants in schizophrenic patients with a depressive syndrome are inconsistent, partially due to methodological reasons.

The careful review from Siris and Bench (89) comes to a more positive conclusion, possibly due to the fact that, based on clinical experience, the authors tried to better understand the implications of methodological problems on the results and, therefore, give a more balanced general outlook: "studies addressing this question have had mixed results, but are generally regarded as being favorable" (89, page 156). This positive view is shared by others (96, 110, 111).

Although the position of the Cochrane metaanalysis (109) might be seen as an overcritical position that does not fit into clinical experience, it has to be accepted that altogether the empirical basis for antidepressant treatment of depressive symptoms in schizophrenia is weak. This example of comedication with antidepressants to treat depressive symptoms in schizophrenia underlines how difficult it is to obtain empirical results in the sense of evidence-based medicine. It is hard to understand why such an important field of drug treatment in schizophrenia is so neglected that it is difficult to draw final conclusions. Apparently this question never attracted the interest of pharmaceutical companies nor public sponsors to perform necessary, well-designed trials on large samples. Such trials would be highly recommended.

To summarize, the results of randomized, controlled studies of the add-on treatment with antidepressants in schizophrenic patients with a depressive syndrome are inconsistent, partially due to methodological reasons. Some studies give positive results, while a major group of studies was negative. In spite of all demands for an evidence-based approach in pharmacopsychiatry, the indication of antidepressants in schizophrenic patients with depressive symptoms seems more driven by clinical experience, which is apparently more positive than by results from RCTs. This also might explain why several important guidelines recommend comedication with antidepressants in schizophrenic patients with a depressive syndrome (112-114).

Conclusions

Depression in the wider sense, or depressive symptoms that fulfill the operationalized, diagnostic criteria for a depressive episode/major depression, can occur at any stage of a schizophrenic psychosis.

It should be discussed further whether these depressive symptoms are part of the rich, psychopathological phenomenology of schizophrenia, which, besides the core paranoid-hallucinatory syndrome, includes a negative syndrome, a cognitive syndrome and a depressive syndrome, or whether depression and schizophrenia should be seen as separate conditions in terms of the concept of comorbidity. Apart from this, the overlap between depressive symptoms and neuroleptic-induced parkinsonian symptoms (akinetic depression), as well as negative symptoms, has to be considered.

Second-generation antipsychotics (SGAs) have antidepressive effects in placebo-controlled studies and seem to have advantages over first-generation antipsychotics (FGAs) in reducing depressive symptoms in the context of schizophrenia. However, the respective results are derived in ex post analyses from studies primarily designed to demonstrate antipsychotic efficacy. Also, other methodological limitations have to be considered, as well as the inconsistency of the results. Definitely there is a need for properly designed prospective studies in this field, insofar as the given clinical recommendation to prioritize the SGAs in this indication is preliminary and has be taken with caution. A special advantage of the SGAs is that apparently they do not induce

depressive symptoms, which is a known side effect of FGAs, described by the concept of pharmacogenetic/neuroleptogenic depression or akinetic depression.

A special advantage of the SGAs is that apparently they do not induce depressive symptoms, which is a known side effect of FGAs, described by the concept of pharmacogenetic/neuroleptogenic depression or akinetic depression.

The efficacy of an add-on treatment with antidepressants, in addition to the ongoing, neuroleptic treatment, is hitherto not best proven in the sense of evidence-based medicine. There are some RCTs with positive results, but altogether the data are inconsistent. Most of these studies involve FGAs, while data on comedication of antidepressants with SGAs are lacking. Somewhat in contrast to the inconsistent results of the respective clinical trials, which might be partially caused by methodological problems, the clinical experience seems to be more positive. This also is reflected in many important guidelines, which recommend comedication with antidepressants for the treatment of depressive symptoms in schizophrenia. The risk of inducing positive symptoms by antidepressants has to be considered, although the evidence is limited in this respect. Furthermore, the risk of pharmacokinetic interactions has to be taken into account, especially when using SSRIs.

Based on these observations, the following principal suggestions for the drug treatment of schizophrenic patients with a depressive syndrome can be given. However, be aware that these suggestions are not fully evidence-based and, at least partially, are more derived from clinical experience:

- If a patient being treated with first-generation antipsychotics (FGAs) develops a depressive syndrome, the reduction of the neuroleptic dose and/or comedication with an anticholinergic might be helpful (especially if the patient has parkinsonian side effects).

- When comedication with an anticholinergic does not lead to a sufficient reduction of the depressive syndrome, comedication with an antidepressive should be tried if a switch to another antipsychotic medication is not for a clinical reason. (Second-generation antipsychotics [SGAs] are prioritized under this condition!) Potential pharmacokinetic interactions should be observed carefully.

- If there are no relevant reasons to continue with the FGA under these conditions, then the switch to an SGA (especially one of those with the lowest EPS risk) is a better option.

- Especially if a schizophrenic patient has a known risk for depressive and/or extrapyramidal side effects under treatment with FGAs, then an SGA is preferable in general to an FGA when selecting an antipsychotic for the treatment of a schizophrenic episode.

- If a schizophrenic patient already has a depressive syndrome, and the decision for differential drug treatment of a schizophrenic episode is pending, an SGA (especially one of those with the lowest EPS profile and the best evidence for antidepressive effects) should be chosen. It hopefully will reduce the psychotic symptoms, as well as the depressive symptoms.

- If the treatment with an SGA does not improve the depressive symptoms in a sufficient way, comedication with an antidepressant should be tried. Potential pharmacokinetic interactions should be observed carefully.

- An antidepressant should never be administrated to a schizophrenic patient with a depressive syndrome without the protection of an antipsychotic, even if the patient suffers at the given time only from depressive and not psychotic symptoms. This procedure is necessary to prevent the potential induction of psychotic symptoms.

- Apart from these detailed recommendations, the more important suggestion is that the prioritization of SGAs in this context is meaningful in two aspects: first, SGAs have a (much) lower risk of inducing pharmacogenic depression/akinetic depression; and secondly, they have better efficacy in reducing depressive symptoms.

A crucial point is the question of when comedication for depressive symptoms should be introduced, i.e., only in cases with a full depressive episode in terms of *ICD-10* or *DSM-IV*, or in subthreshold conditions or at a certain depression score such as 18 points in a HAM-D rating. Finally, in addition to all categorical or dimensional criteria, the suffering of the individual patient should guide the doctor in his/her decision.

As a final point, this review is focused only on drug treatment. Of course, as always in psychiatric treatment, the psychosocial aspects and the possibility of psychosocial intervention have to be considered in addition to the psychopharmacological aspects.

References

1. Wassink TH, Flaum M, Nopoulos P, Andreasen NC. Prevalence of depressive symptoms early in the course of schizophrenia. Am J Psychiatry 1999;156(2):315-316.
2. Bottlender R, Strauss A, Möller HJ. Prevalence and background factors of depression in first admitted schizophrenic patients. Acta Psychiatr Scand 2000;101(2):153-160.
3. an der Heiden W, Konnecke R, Maurer K, Ropeter D, Hafner H. Depression in the long-term course of schizophrenia. Eur Arch Psychiatry Clin Neurosci 2005;255(3):174-184.
4. Birchwood M, Iqbal Z, Upthegrove R. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. Eur Arch Psychiatry Clin Neurosci 2005;255(3):202-212.
5. Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M. The early course of schizophrenia and depression*. Eur Arch Psychiatry Clin Neurosci 2005;255(3):167-173.
6. Krabbendam L, van Os J. Affective processes in the onset and persistence of psychosis. Eur Arch Psychiatry Clin Neurosci 2005;255(3):185-189.
7. Hausmann A, Fleischhacker WW. Depression in patients with schizophrenia. Prevalence, and diagnostic and treatment considerations. CNS Drugs 2000;14(4):289-299.
8. Johnson DA. Depressions in schizophrenia: some observations on prevalence, etiology, and treatment. Acta Psychiatr Scand Suppl 1981;291:137-144.
9. Johnson DA. Studies of depressive symptoms in schizophrenia. Br J Psychiatry 1981;139:89-101.
10. Gross G, Huber G. [Depressive syndromes in the course of schizophrenia (author's transl).] Fortschr Neurol Psychiatr Grenzgeb 1980;48(8):438-446. German.
11. Sands JR, Harrow M. Depression during the longitudinal course of schizophrenia. Schizophr Bull 1999;25(1):157-171.
12. Martin RL, Cloninger CR, Guze SB, Clayton PJ. Frequency and differential diagnosis of depressive syndromes in schizophrenia. J Clin Psychiatry 1985;46(11 Pt 2):9-13.
13. Jäger M, Riedel M, Schmauss M, Pfeiffer H, Laux G, Naber D, et al. Depression during an acute episode of schizophrenia or schizophreniform disorder and its impact on treatment response. Psychiatry Res. In press 2007.
14. Jäger M, Bottlender R, Strauss A, Möller HJ. Fifteen-year follow-up of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition depressive disorders: the prognostic significance of psychotic features. Compr Psychiatry 2005;46(5):322-327.
15. Bottlender R, Hampel H, Sievers M, Möller HJ. [Diagnostics and therapy of depressive symptoms in schizophrenic patients.] MMW Fortschr Med 2005;147 Spec No 2:59-62. German.
16. Addington DE, Addington JM. Attempted suicide and depression in schizophrenia. Acta Psychiatr Scand 1992;85(4):288-291.
17. Conley RR, Ascher-Svanum H, Zhu B, Faries D, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. Schizophr Res 2007;90(1-3):186-197.
18. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, et al.; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003;60(1):82-91.
19. Knights A, Hirsch SR. "Revealed" Depression and drug treatment for schizophrenia. Arch Gen Psychiatry 1981;38(7):806-811.
20. Möller HJ, von Zerssen D. Depressive states occurring during the neuroleptic treatment of schizophrenia. Schizophr Bull 1982;8(1):109-117.
21. Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. Am J Psychiatry 1993;150(11):1643-1648.
22. Nakaya M, Ohmori K, Komahashi T, Suwa H. Depressive symptoms in acute schizophrenic inpatients. Schizophr Res 1997;25(2):131-139.
23. Zisook S, McAdams LA, Kuck J, Harris MJ, Bailey A, Patterson TL, et al. Depressive symptoms in schizophrenia. Am J Psychiatry 1999;156(11):1736-1743.
24. Baynes D, Mulholland C, Cooper SJ, Montgomery RC, MacFlynn G, Lynch G, et al. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. Schizophr Res 2000;45(1-2):47-56.
25. Birchwood M, Iqbal Z, Chadwick P, Trower P. Cognitive approach to depression and suicidal thinking in psychosis. 1. Ontogeny of post-psychotic depression. Br J Psychiatry 2000;177:516-521.
26. Hausmann A, Fleischhacker WW. Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review. Acta Psychiatr Scand 2002;106(2):83-96.
27. Heinrich K. [On the significance of post-remissive exhaustion-syndrome for the rehabilitation of schizophrenics.] Nervenarzt 1967;38(11):487-491. German.
28. McGlashan TH, Carpenter WT Jr. Postpsychotic depression in schizophrenia. Arch Gen Psychiatry 1976;33(2):231-239.
29. Siris SG. Depression in schizophrenia: perspective in the era of "Atypical" antipsychotic agents. Am J Psychiatry 2000;157(9):1379-1389.
30. Bressan RA, Chaves AC, Pilowsky LS, Shirakawa I, Mari JJ. Depressive episodes in stable schizophrenia: critical evaluation of the DSM-IV and ICD-10 diagnostic criteria. Psychiatry Res 2003;117(1):47-56.
31. Fish F. The unitary psychosis - a neurophysiological model. Confin Psychiatr 1963;23:155-170.
32. van Renynghe de Voxvrie G. [Reactualization of the concept of unitary psychosis introduced by Joseph Guislain.] Acta

Psychiatr Belg 1993;93(4):203-219. French.

33. Lapierre YD. Schizophrenia and manic-depression: separate illnesses or a continuum? Can J Psychiatry 1994;39(9 Suppl 2):S59-S64.

34. Maier W, Hofgen B, Zobel A, Rietschel M. Genetic models of schizophrenia and bipolar disorder: overlapping inheritance or discrete genotypes? Eur Arch Psychiatry Clin Neurosci 2005;255(3):159-166.

35. Angst J. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. Schizophr Res 2002;57(1):5-13.

36. Möller HJ. Antipsychotic and antidepressive effects of second generation antipsychotics: two different pharmacological mechanisms? Eur Arch Psychiatry Clin Neurosci 2005;255(3):190-201.

37. Rifkin A, Quitkin F, Klein DF. Akinesia: a poorly recognized drug induced extrapyramidal behavioral disorder. Arch Gen Psychiatry 1975;32:672-674.

38. Van Putten T, May RP. "Akinetic depression" in schizophrenia. Arch Gen Psychiatry 1978;35(9):1101-1107.

39. Carpenter WT Jr, Heinrichs DW, Alphs LD. Treatment of negative symptoms. Schizophr Bull 1985;11(3):440-452.

40. Siris SG, Morgan V, Fagerstrom R, Rifkin A, Cooper TB. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. Arch Gen Psychiatry 1987;44(6):533-539.

41. Siris SG, Adan F, Cohen M, Mandeli J, Aronson A, Casey E. Postpsychotic depression and negative symptoms: an investigation of syndromal overlap. Am J Psychiatry 1988;145(12):1532-1537.

42. Siris SG, Bermanzohn PC, Gonzalez A, Mason SE, White CV, Shuwall MA. The use of antidepressants for negative symptoms in a subset of schizophrenic patients. Psychopharmacol Bull 1991;27(3):331-335.

43. Möller HJ. Clinical evaluation of negative symptoms in schizophrenia. Eur Psychiatry 2007;22(6):380-386.

44. Addington D, Addington J, Atkinson M. A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Schizophr Res 1996;19(2-3):205-212.

45. Möller HJ. Scales used in depression and anxiety research. In: Kasper S, den Boer JA, Ad Sitsen JM, editors. Handbook of depression and anxiety: a biological approach. 2nd ed. New York: Informa Healthcare; 2003. p. 789-808.

46. Häfner H, Loffler W, Maurer K, Hambrecht M, an der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. Acta Psychiatr Scand 1999;100(2):105-118.

47. Helmchen H, Hippius H. [Depressive syndrome in the course of neuroleptic therapy.] Nervenarzt 1967;38(10):455-458. German.

48. Helmchen H, Hippius H. Pharmakogene depression. In: Hippius H, Selbach H, editors. Das depressive syndrom. München: Urban und Schwarzenberg; 1962.

49. Möller HJ, von Zerssen D. Depression in schizophrenia. In: Burrows GD, Norman TR, Rubinstein G, editors. Handbook of studies on schizophrenia, part 1, epidemiology, aetiology and clinical features. Amsterdam: Elsevier; 1986. p. 183-191.

50. Möller HJ, von Zerssen D. Depressive states occurring during the neuroleptic treatment of schizophrenia. Schizophr Bull 1982;8(1):109-117.

51. Möller HJ, Schmid-Bode W, von Zerssen D. Prediction of long-term outcome in schizophrenia by prognostic scales. Schizophr Bull 1986;12(2):225-234.

52. Möller HJ, Scharl W, von Zerssen D. [Prediction of therapeutic success in acute neuroleptic treatment: results of an empirical study of 243 inpatient-treated schizophrenic patients.] Fortschr Neurol Psychiatr 1985;53(10):370-383. German.

53. Möller HJ. Occurrence and treatment of depressive comorbidity/cosyndromality in schizophrenic psychoses: conceptual and treatment issues. World J Biol Psychiatry 2005;6(4):247-263.

54. Möller HJ. Antidepressive effects of traditional and second generation antipsychotics: a review of the clinical data. Eur Arch Psychiatry Clin Neurosci 2005;255(2):83-93.

55. Möller HJ. Amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(7):1101-1111.

56. Davies LM, Lewis S, Jones PB, Barnes TR, Gaughran F, Hayhurst K, et al. Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. Br J Psychiatry 2007;191:14-22.

57. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000;321(7273):1371-1376.

58. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154(4):457-465.

59. Tollefson GD, Sanger TM, Beasley CM, Tran PV. A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998;43(11):803-810.

60. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55(3):250-258.

61. Marder SR, Davis JM, Chouinard G. The effects of risperi-

done on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58(12):538-546.

62. Peuskens J, Van Baelen B, De Smedt C, Lemmens P. Effects of risperidone on affective symptoms in patients with schizophrenia. Int Clin Psychopharmacol 2000;15(6):343-349.

63. Müller MJ, Wetzel H, Eich FX, Rein W, Puech A, Benkert O; Amisulpride Study Group. Dose-related effects of amisulpride on five dimensions of psychopathology in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol 2002;22(6):554-560.

64. Peuskens J, Möller HJ, Puech A. Amisulpride improves depressive symptoms in acute exacerbations of schizophrenia: comparison with haloperidol and risperidone. Eur Neuropsychopharmacol 2002;12(4):305-310.

65. Emsley RA, Buckley P, Jones AM, Greenwood MR. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. J Psychopharmacol 2003;17(2):210-215.

66. Keck P Jr, Buffenstein A, Ferguson J, Feighner J, Jaffe W, Harrigan EP, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998;140(2):173-184.

67. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. Neuropsychopharmacology 1999;20(5):491-505.

68. Hirsch SR, Kissling W, Bauml J, Power A, O'Connor R. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002;63(6):516-523.

69. Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol 2003;6(4):325-337.

70. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001;158(5):765-774.

71. Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161(10):1837-1847.

72. Vanelle JM, Douki S. A double-blind randomised comparative trial of amisulpride versus olanzapine for 2 months in the treatment of subjects with schizophrenia and comorbid depression. Eur Psychiatry 2006;21(8):523-530.

73. Kinon BJ, Lipkovich I, Edwards SB, Adams DH, Ascher-Svanum H, Siris SG. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. J Clin Psychopharmacol 2006;26(2):157-162.

74. Schmidt AW, Lebel LA, Howard HR Jr, Zorn SH. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425(3):197-201.

75. Möller HJ, Muller H, Borison RL, Schooler NR, Chouinard G. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. Eur Arch Psychiatry Clin Neurosci 1995;245(1):45-49.

76. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162(7):1351-1360.

77. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26(6):600-609.

78. Enns MW, Swenson JR, McIntyre RS, Swinson RP, Kennedy SH; CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders. VII. Comorbidity. Can J Psychiatry 2001;46(Suppl 1):77S-90S.

79. Heinrich K. [Aimed symptom provocation with monoamineoxidases in the diagnosis and therapy of schizophrenic psychoses.] Nervenarzt 1960;31:507-512. German.

80. Prusoff BA, Williams DH, Weissman MM, Astrachan BM. Treatment of secondary depression in schizophrenia. A double-blind, placebo-controlled trial of amitriptyline added to perphenazine. Arch Gen Psychiatry 1979;36(5):569-575.

81. Kramer MS, Vogel WH, DiJohnson C, Dewey DA, Sheves P, Cavicchia S, et al. Antidepressants in 'depressed' schizophrenic inpatients. A controlled trial. Arch Gen Psychiatry 1989;46(10):922-928.

82. Vandel B, Vandel S, Allers G, Bechtel P, Volmat R. Interaction between amitriptyline and phenothiazine in man: effect on plasma concentration of amitriptyline and its metabolite nortriptyline and the correlation with clinical response. Psychopharmacology (Berl) 1979;65(2):187-190.

83. Nelson JC, Jatlow PI. Neuroloeptic effect on desipramine steady-state plasma concentratins. Am J Psychiatry 1980;137(10):1232-1234.

84. Centorrino F, Baldessarini RJ, Frankenburg FR, Kando J, Volpicelli SA, Flood JG. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. Am J Psychiatry 1996;153(6):820-822.

85. Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry 1996;57(Suppl 11):12-25.

86. Möller HJ. Non-neuroleptic approaches to treating negative symptoms in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2004;254(2):108-116.

87. Wetzel H, Anghelescu I, Szegedi A, Wiesner J, Weigmann H, Harter S, et al. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. J Clin Psychopharmacol 1998;18(1):2-9.

88. Becker RE. Implications of the efficacy of thiothixene and a chlorpromazine-imipramine combination for depression in schizophrenia. Am J Psychiatry 1983;140(2):208-211.

89. Siris SG, Bench C. Depression and schizophrenia. In: Hirsch SR, Weinberger DR, editors. Schizophrenia. Oxford (UK): Blackwell Publishing; 2003. p. 142-167.

90. Kennedy RE, Miller JJ. Amitriptyline-perphenazine in the treatment of schizophrenia. Am J Psychiatry 1963;119:1092-1093.

91. Rada RT, Donlon PJ. Depression and the acute schizophrenic process. Psychosomatics 1975;16(3):116-119.

92. Gibbon J. Some examples of the combined use of psychotropic agents. Dis Nerv Syst 1961;22(4)(Suppl):81-85.

93. Ayd FJ Jr. Amitriptyline: reappraisal after six years experience. Dis Nerv Syst 1965;26(11):719-727.

94. Bowes HA. Amitriptyline, perphenazine and psychotherapy. Combined therapy in 800 patients over four years. Psychosomatics 1967;8(1):1-3.

95. Keskiner A. A long-term follow-up of fluphenazine enanthate treatment. Curr Ther Res Clin Exp 1973;15(6):305-313.

96. Plasky P. Antidepressant usage in schizophrenia. Schizophr Bull 1991;17(4):649-657.

97. Hogarty GE, McEvoy JP, Ulrich RF, DiBarry AL, Bartone P, Cooley S, et al. Pharmacotherapy of impaired affect in recovering schizophrenic patients. Arch Gen Psychiatry 1995;52(1):29.

98. Singh AN, Saxena B, Nelson HL. A controlled clinical study of trazodone in chronic schizophrenic patients with pronounced depressive symptomatology. Curr Ther Res 1978;23:485-501.

99. Waehrens J, Gerlach J. Antidepressant drugs in anergic schizophrenia. A double-blind cross-over study with maprotiline and placebo. Acta Psychiatr Scand 1980;61(5):438-444.

100. Kurland AA, Nagaraju A. Viloxazine and the depressed schizophrenic--methodological issues. J Clin Pharmacol 1981;21(1):37-41.

101. Dufresne RL, Kass DJ, Becker RE. Bupropion and thiothixene versus placebo and thiothixene in the treatment of depression in schizophrenia. Drug Dev Res 1988;12:259-266.

102. Müller-Siecheneder F, Müller MJ, Hillert A, Szegedi A, Wetzel H, Benkert O. Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Pharmacol 1998;18(2):111-120.

103. Siris SG, Bermanzohn PC, Mason SE, Shuwall MA. Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. Arch Gen Psychiatry 1994;51(2):109-115.

104. Cooper SJ, Mulholland C, Lynch G, Baynes D, King DJ. Sertraline in the treatment of depressive symptoms in stable, chronic schizophrenia: A placebo controlled trial. Schizophr Res 2000;41(1):209.

105. Vlokh I, Mikhnyak S, Kachura O. Zoloft in management of depression in schizophrenia. Schizophr Res 2000;41(1):209.

106. Salokangas RK, Saarijarvi S, Taiminen T, Kallioniemi H, Lehto H, Niemi H, et al. Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. Acta Psychiatr Scand 1996;94(3):175-180.

107. Goff DC, Brotman AW, Waites M, McCormick S. Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. Am J Psychiatry 1990;147(4):492-494.

108. Siris SG, Addington D, Azorin JM, Falloon IR, Gerlach J, Hirsch SR. Depression in schizophrenia: recognition and management in the USA. Schizophr Res 2001;47(2-3):185-197.

109. Whitehead C, Moss S, Cardno A, Lewis G. Antidepressants for people with both schizophrenia and depression. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.:CD002305. DOI: 10.1002/14651858.CD002305

110. Levinson DF, Umapathy C, Musthaq M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. Am J Psychiatry 1999;156(8):1138-1148.

111. Taiminen T, Syvälahti E, Saarijärvi S, Niemi H, Lehto H, Ahola V, et al. Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. Int Clin Psychopharmacol 1997;12(1):31-35.

112. Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller HJ; WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: long-term treatment of schizophrenia. World J Biol Psychiatry 2006;7(1):5-40.

113. Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller HJ; WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. World J Biol Psychiatry 2005;6(3):132-191.

114. Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. Am J Psychiatry 1997;154(4 Suppl):1-63.