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ORIGINAL PAPER

Hans-Jürgen Möller

Non-neuroleptic approaches to treating negative symptoms in schizophrenia

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Abstract The novel/atypical neuroleptics have proven to be effective in treating negative symptoms but although clinical experience appears to show that they have advantages over the traditional neuroleptics in treating negative symptoms, superiority has not always been statistically confirmed and the treatment results in individual patients in everyday clinical practice are often not satisfying. Therefore other drug treatment options also have to be carefully considered.

This paper presents a systematic review of non-neuroleptic drug treatments for negative symptoms in schizophrenia, based on MEDLINE searches in the databases from 1995 to September 2002 to identify pertinent clinical trials. Relevant literature was also found in the reference lists of papers identified by the MEDLINE searches.

Most of the alternatives to neuroleptics have only been investigated as add-on therapies and not as monotherapies. The SSRIs seem to have a certain place in the treatment of negative symptoms. Anticonvulsants, oestrogens and glutamatergic drugs can currently only be seen as experimental drugs and require further empirical evaluation.

Key words negative symptoms · schizophrenia · antidepressants · oestrogens · anticonvulsants

Introduction

Negative symptoms play an important role in schizophrenia and are related to deficits in global functioning and global outcome (Bottlender et al. 1999, 2001; Möller et al. 2002). They should therefore be a major focus in the treatment of schizophrenia.

Reviews of the results of controlled studies on the efficacy of the new/atypical neuroleptics in treating negative symptoms show that in general these antipsychotics have a better effect than the classical neuroleptics on the negative symptoms of acute schizophrenic patients. However, all together the advantages of novel or atypical neuroleptics in negative symptoms as compared to classical neuroleptics are generally limited and often not satisfying in individual patients (Möller 1999, 2000 a, 2000 b). It is therefore necessary to look for alternative or additional drug treatment possibilities.

The following paper reviews the current empirical findings in this field, especially with respect to antidepressants, and antiepileptic and glutamatergic drugs. Although in everyday clinical practice psychosocial treatments are indicated in combination with drug treatments for the negative symptoms of schizophrenia, these will not be discussed as this review only considers pharmacological approaches. The reader is referred to the relevant literature on this subject (Anonymous 1999; Heinssen et al. 2000; Lehman and Steinwachs 1998).

Antidepressants in the treatment of negative symptoms

The role of antidepressant drugs as an adjunct in the treatment of schizophrenic patients with negative symptoms remains unclear. The findings of the few studies that have investigated this therapeutic option – most of them were performed with selective serotonin reuptake inhibitors (SSRIs) –, are inconsistent and not of the highest methodological level (Becker 1983; Plasky 1991; Silver and Nassar 1992; Siris et al. 1991; Waehrens and Gerlach 1980). Although most of these studies used a double-blind, placebo-controlled design, they have several problems, for example small sample size and consequent lack of statistical power (most studies included a total of only about 30 patients). Furthermore,

Prof. H.-J. Möller
Dept. of Psychiatry
Ludwig-Maximilians-University
Nussbaumstrasse 7
80336 Munich, Germany
Tel.: +49-89/5160-5501
Fax: +49-89/5160-5522
E-Mail: hans-juergen.moeller@med.uni-muenchen.de

some of them did not focus on patients with predominant, stable negative symptoms (Möller et al. 1994), but included patients with an acute episode of schizophrenia who had not responded well to the initial treatment or initial treatment sequences. In some of the studies the focus was also not specifically on negative symptoms but on the more general question of an augmentation effect on several psychopathological domains. In some studies the relationship between improvement of negative and depressive symptoms was not explored carefully enough (Möller et al. 1995).

Only a few of the studies will be described in more detail below to give an impression of the kind and quality of the studies and the results.

The selective serotonin reuptake inhibitors (SSRIs) have been investigated more intensively because of their better tolerability compared with classical tricyclics and their reduced risk of pharmacodynamic interactions, in addition to theoretical reasons (i. e. the hypothesis that serotonin may be involved in the pathophysiology of schizophrenia). This hypothesis is supported by studies of postmortem tissue, functional imaging, receptor binding to serotonergic receptors, the infusion of serotonergic agents and serotonin/dopamine interactions in preclinical models (Breier 1995; Kapur and Remington 1996). These studies have provided a strong theoretical basis for examining the effects of serotonergic drugs as therapeutic agents in schizophrenia in general, not just for the treatment of negative symptoms. $5HT_2$ receptor antagonists appear to have therapeutic efficacy for negative symptoms, as was demonstrated for ritanserin, a $5HT_{2A}$ antagonist, the forerunner of risperidone (Gelders et al. 1986; Leysen et al. 1993). It may seem contradictory that SSRIs should produce an effect similar to a serotonin antagonist. However, both types of agents have antidepressant effects (Reyntjens et al. 1986) and some evidence suggests a complementary relationship between $5HT_2$ blockade and $5HT_1$ receptor activation (Backus et al. 1990). Hashimoto and colleagues (1993) found evidence of increased $5HT_{1A}$ receptor binding and decreased $5HT_2$ receptor binding in postmortem brains of schizophrenic patients compared to controls. Ugedo and colleagues (Ugedo et al. 1989) demonstrated that the stimulatory effect of $5HT_2$ antagonists upon midbrain dopaminergic receptors requires the presence of 5HT.

Silver and Nassar were the first group to demonstrate an effect of an SSRI when given as an adjunctive treatment in negative symptoms. In a 6-week, placebo-controlled study on 30 inpatients with chronic schizophrenia, they demonstrated that fluvoxamine can improve negative symptoms when added to ongoing antipsychotic treatment (Silver and Nassar 1992). Since then, evidence has accumulated that SSRI augmentation of typical and atypical antipsychotics may be useful in treating negative symptoms of schizophrenic patients. The authors proposed that the effectiveness of SSRI augmentation is specifically linked to serotonergic action, leading to a modulation of the serotonergic-dopaminergic balance. Silver and Shmugliakov found further proof for this hypothesis in their 6-week study that compared 100 mg/day fluvoxamine with 100 mg/day maprotiline as an add-on therapy (Silver and Shmugliakov 1998). In this study 38 schizophrenic patients, all of whom were receiving typical antipsychotic medications, fulfilled the DSM-III-R criteria for chronic schizophrenia with at least two years of illness and had at least a moderate score on one of the global scales of the Scale for the Assessment of Negative Symptoms (SANS), were randomised to treatment with either fluvoxamine or maprotiline. Five patients (38.5 %) in the fluvoxamine group and none in the maprotiline group were responders (defined as a reduction of 20 % or more in the total SANS score). In addition, compared with baseline the SANS total scores were significantly lower after 6 weeks' treatment with fluvoxamine but did not change with maprotiline. The difference in the SANS scores between the two groups after six weeks was significant, again in favour of the fluvoxamine group. Changes in the MADRS score showed significant correlations with changes in the total SANS score ($r = 0.70$), but there was no significant correlation between change in the MADRS score and change in any of the five subscale scores of the SANS or with the negative factor of the BPRS (Silver and Shmugliakov 1998).

Two uncontrolled trials including a total of 17 schizophrenic patients reported significant clinical improvement associated with the addition of fluoxetine 20 mg/day to a stable dose of neuroleptic (Goff et al. 1990; Goldman and Janecek 1990). Goff et al. (1995) published the results of a placebo-controlled study of fluoxetine as an adjunctive treatment in negative symptoms. After a two-week placebo lead-in, 41 schizophrenic inpatients were randomly assigned to fluoxetine 20 mg/day or placebo added to a depot neuroleptic for a 6-week double-blind trial. All patients had received a stable dose of depot neuroleptic for at least six months and did not meet criteria for depression. The comparison of clinical ratings at week 6, controlling for baseline scores, demonstrated significantly greater reductions in the negative symptoms subscale (BPRS) in patients receiving fluoxetine compared with placebo. Fluoxetine produced a mean reduction in negative symptoms of 23 % versus 12 % with placebo. No other outcome measures differed significantly between the two groups, although at week 6 the depression subscale score of the BPRS decreased by 26 % in patients receiving fluoxetine versus 4 % in the placebo group. The reduction in negative symptoms did not correlate with changes in depression or extrapyramidal symptoms (Fig. 1) (Goff et al. 1995).

Positive results of an adjunctive fluoxetine treatment of negative symptoms in chronic schizophrenic patients were also reported by Spina et al. (1994). They performed a placebo-controlled, double-blind, 12-week study in 34 chronic schizophrenic inpatients who were on stable treatment with neuroleptics for at least four weeks. The patients were diagnosed according to DSM-III-R as

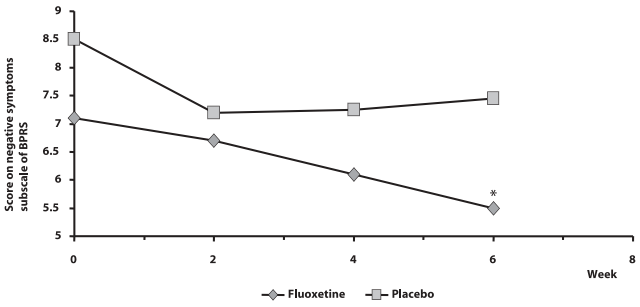

Fig. 1 Change in negative symptoms subscale in schizophrenic patients treated with fluoxetine or placebo in addition to a stable dose of neuroleptics. *p = 0.03 versus placebo (Goff et al. 1995)

having chronic schizophrenia with a history of at least five years of illness, a score of at least moderate on one of the five global subscales of the SANS at the baseline assessment and a baseline total score lower than 20 on the Hamilton Rating Scale for Depression (HAMD), in order to exclude the presence of a major depressive disorder. Negative symptoms, as measured by change on the SANS at the endpoint compared to baseline values, were significantly improved in fluoxetine-treated patients, but not in the placebo group. There was also a slight but statistically significant decrease in depressive symptoms, as measured by the HAMD. At the final evaluation a mean 34 % decrease in the SANS total score was observed in the fluoxetine group, while no appreciable modifications were evident in the placebo group. Positive symptoms remained unchanged in this study.

Another study evaluated augmentation with fluoxetine in clozapine-treated patients (Buchanan et al. 1996) who, despite adequate treatment with clozapine, continued to exhibit persistent positive or negative symptoms. In this double-blind, 8-week study, no significant differences in positive, negative or depressive symptoms between patients given adjunctive fluoxetine treatment (20 mg/day) or placebo could be found.

In a further study by the same research group (Arango et al. 2000), 20 mg/day fluoxetine was tested in 32 patients as an adjunct to their neuroleptic drug regimen over an 8-week, double-blind treatment phase. The patients had been enrolled in the outpatient clinic for a minimum of six months, were judged to be clinically stable, and had taken the same dose of antipsychotic for a minimum of one month. There were no significant differences between the active and placebo group on any of the psychopathological variables (BPRS positive symptom score, BPRS negative symptom score, SANS total score, Hamilton depression scale).

A double-blind, add-on study testing the SSRI citalopram (20–40 mg/day) as an adjuvant in 90 patients with chronic schizophrenia failed to show superiority to placebo with respect to either the PANNS total score or the negative score. A response was only seen in the PANNS subscore depression/anxiety (Taiminen et al. 1997). Similarly, also a placebo-controlled study on 36 patients with 50 mg/day sertraline as an adjunctive treatment failed to demonstrate efficacy in negative symptoms or in other PANNS dimensions (Lee et al. 1998).

Mirtazapine has an interesting psychopharmacological profile, having antagonistic effects at serotonin $5HT_2$ and $5HT_3$ receptors and indirect agonistic effects on the $5HT_{1a}$ receptor as well as adrenergic α_2 antagonistic effects. There are animal data suggesting that mirtazapine may enhance the antipsychotic effects of haloperidol as well as reduce its extrapyramidal side effects (Berendsen et al. 1998). Thirty schizophrenic patients were randomised to either mirtazapine or placebo. Berk et al. (2001) investigated mirtazapine as an add-on therapy to haloperidol in the treatment of negative symptoms in a 6-week, double-blind, randomised, placebo-controlled study. Patients met the DSM-IV criteria for schizophrenia and were treated with haloperidol 5 mg/day. In addition, they received under placebo-controlled conditions 30 mg mirtazapine daily for a trial period of six weeks. A robust effect of mirtazapine in reducing negative symptoms of schizophrenic patients could be demonstrated. At the end of the trial the PANSS negative scale scores were 42 % lower in the mirtazapine than in the placebo group. Although there was an effect on the HAMD at weeks 2 and 4, at endpoint there were no significant differences between the groups on the depression score. No difference emerged between mirtazapine and placebo on the positive subscale of the PANSS, or with respect to extrapyramidal side effect measured by the Simpson-Angus Scale. These latter results suggest that the positive effect on negative symptoms was apparently not influenced by an effect on depressive symptoms or on extrapyramidal side effects (Berk et al. 2001).

As to classical tricyclics there are only few data from older studies. Siris and colleagues (Siris et al. 1991) studied stable, depressed schizophrenic patients with minimal productive symptoms in a placebo-controlled study with imipramine, whereby imipramine was added to an ongoing treatment with depot neuroleptics. They reported an improvement in depression and in negative symptoms (although the latter were not the focus of the study!). Waehrens and Gerlach (1980) were not able to demonstrate an improvement of negative symptoms in a double-blind, cross-over study on 20 patients. The tetracyclic antidepressant maprotiline was given as adjunctive therapy to the ongoing neuroleptic medication.

To summarise, the body of evidence for a relevant effect of antidepressants in negative symptoms is weak. Nevertheless some studies gave a positive signal, although the sample size was small (Plasky 1991; Silver and Nassar 1992; Siris et al. 1991). The clear positive results of some of these trials indicate that especially fluoxetine, fluvoxamine and also mirtazapine (only one study) might be a meaningful approach as an adjunctive treatment for patients with negative symptoms. A positive result might depend on special selection of patients and, under routine clinical conditions, this adjunctive therapy might be an option for at least some patients and should therefore be explored on an individual basis.

However, two aspects must be carefully considered when using antidepressants as adjunctive therapy. The first is that in trials using antidepressants for the treatment of depressive symptoms or negative symptoms in schizophrenia, it has been described that the improvement of the positive symptoms might be delayed and/or that a relapse of positive symptoms can occur in patients who already had a partial full remission of psychotic symptoms (Kramer et al. 1989; Prusoff et al. 1979). To avoid this kind of risk, antidepressants in schizophrenic patients should never be administered as monotherapy but always in combination with neuroleptic medication.

Another problem of treatment with antidepressants in combination with neuroleptics is the risk of possible pharmacodynamic and/or pharmacokinetic interactions. Particularly the pharmacokinetic consequences of the combination of SSRIs and neuroleptics should be carefully considered. This combination may result in an increase of the neuroleptic serum level, which may be quite extreme under certain conditions, e. g. the combination of fluvoxamine and clozapine. The increase of the serum level of the neuroleptics has potential clinical consequences, especially in the sense of unwanted effects (Centorrino et al. 1994; Goff et al. 1991, 1995).

Anticonvulsants as comedication

The so-called "excitotoxic hypothesis" of schizophrenia suggests that at least in a subtype of schizophrenia, progressive excitotoxic neuronal cell death in hippocampal and cortical areas occurs via disinhibition of glutamatergic projections to these areas (Deutsch et al. 2001). Patients belonging to this subgroup would be expected to have poor outcomes characterised by pronounced negative symptoms and cognitive deficits and profound psychosocial deterioration, and possibly also by evidence of progressive neurodegeneration. Disinhibited glutamatergic activity could result from inhibition of NMDA receptor-mediated neurotransmission and a consequent failure to stimulate inhibitory GABAergic interneurons and/or anatomic degeneration of inhibitory GABAergic interneurons. The result of these hypothesised mechanisms is excessive stimulation of the AMPA/kainate class of glutamate receptor complexes. Interventions based on this hypothesis include facilitation of NMDA receptor-mediated neurotransmission or potentiation of GABAergic neurotransmission. In this context it should also be mentioned that there is evidence from postmortem studies describing a deficient inhibitory neurotransmission of GABA in schizophrenia, which recently was also supported by an in vivo benzodiazepine receptor binding study showing significant correlations between the severity of positive or negative symptoms and limbic cortical areas: positive symptoms were negatively correlated with [^{123}I]iomazenil receptor binding in the left medial temporal region, negative symptoms were inversely related to iomazenil receptor binding in the medial frontal region (Busatto et al. 1997). Based on this theoretical background, anticonvulsant drugs with a known GABAergic property were tested in schizophrenia as an add-on therapy; however, for the most part these studies were not conducted in schizophrenia with primarily negative symptoms.

Beside its GABAergic properties, carbamazepine inhibits the Ca-calmodulin system through its inhibitory effect on Ca-activated protein kinases (DeLorenzo 1983). Thus it may have the same positive effect that diphenylbutylpiperidines, such as pimozide, seem to have on negative symptomatology through calcium channel inhibition (Feinberg et al. 1988; Gould et al. 1983). Carbamazepine has the presumed ability to act as a vasopressin agonist (Gold et al. 1983), and vasopressin has been shown to significantly improve negative symptoms (Brambilla et al. 1988). Carbamacapine also increases dopamine in brain slices (Barros et al. 1986), and may therefore enhance dopamine hypofunction in the frontal region, one of the mechanisms postulated as underlying negative symptomatology (Nachshoni et al. 1994).

Carbamazepine has been evaluated as an adjunct to neuroleptic treatment in acute schizophrenic and schizoaffective disorders (Dose et al. 1987). As shown by a recent meta-analysis (Leucht et al. 2002), all together there seems to be a weak trend for a better improvement of global schizophrenic symptomatology, and possibly also for positive and negative symptoms. Apparently this small effect cannot only be explained by the inclusion of schizoaffective patients in some of these studies. Altogether the total number of patients involved in the placebo-controlled studies was small (about 250 patients). When using this add-on strategy, the pharmacokinetic interaction of carbamazepine, which leads to a decrease in serum levels of haloperidol and other neuroleptics, has to be taken into consideration because it is of such a degree that it can induce treatment failures (Hesslinger et al. 1999). Few of these studies focussed on treatment-resistant schizophrenia, and only the study by Nachshoni et al. (1994) investigated residual schizophrenia with predominant negative symptoms. Twenty-eight residual schizophrenics hospitalised in a chronic institution with a 9- to 30-year history of disease with predominantly negative symptoms were given carbamazepine as an add-on therapy to the ongoing medication with classical neuroleptics. Carbamazepine was administered in a double-blind trial and therapeutic effects were measured by the SANS. Patients were also assessed for positive symptoms using the BPRS, for depression using the HAMD scale, and for extrapyramidal symptoms by the Simpson-Angus scale, to rule out these symptoms as sources of secondary negative symptoms. The study continued for seven weeks with therapeutic carbamazepine levels achieved during the last five weeks. There was no significant positive effect of carbamazepine on negative symptoms (Nachshoni et al. 1994). This negative result has to be interpreted in the context that the patients were extremely, chronically ill.

Valproate, in different preparations, was only tested as an add-on therapy in schizophrenia in two very small

pilot studies, from which relevant conclusions cannot be drawn (Hesslinger et al. 1999; Wassef et al. 2000). Despite this limitation, in the placebo-controlled, double-blind study by Wassef et al. (2000) a positive effect on negative symptoms was described. The authors suggested that comedication with divalproex sodium might be effective in relieving the symptoms of acute schizophrenia.

Topiramate has a pharmacological mechanism that includes potentiation of GABAergic neurotransmisison and antagonism of KA/AMPA receptors. In a recent case report, topiramate was administered for a period of 12 weeks to a stable regimen with antipsychotic medication. The topiramate dosage was adjusted to the maximal tolerated dose. A "dramatic" response of negative symptoms was observed in this case report (Drapalski et al. 2001).

Thus at the moment there is no clear evidence for the efficacy of anticonvulsants in the comedication of negative symptoms. However, their potential has not yet been investigated intensively enough.

Drugs related to the glutamate system

Glutamatergic neurones are the major excitatory pathway linking the cortex, limbic system and thalamus, regions that are hypothetically implicated in schizophrenia. Postmortem studies have revealed alterations in pre- and post-synaptic markers for glutamatergic neurones in several brain regions in schizophrenia. The N-methyl-D-aspartic acid (NMDA) subtype of the glutamate receptor may be particularly important as blockade of this receptor by the dissociative anaesthetics (like phencyclidine and ketamine) reproduces in normal subjects the symptomatic manifestations of schizophrenia, including negative symptoms and cognitive impairments (Malhotra et al. 1996; Möller and Husby 2000; Newcomer et al. 1999), and increases dopamine release in the mesolimbic system (Bowers et al. 1987; Deutch et al. 1987; Verma and Moghaddam 1996). Thus hypofunction of a subpopulation of corticolimbic NMDA receptors may participate in the pathophysiology underlying schizophrenia, including negative symptoms (Carfagno et al. 2000; Goff and Coyle 2001; Krystal et al. 1999; Tsai and Coyle 2002). However, the results of studies performed in the field of negative symptoms of schizophrenia with different glutamatergic agents are quite controversial. The methodological problems are similar to those mentioned concerning studies on an add-on therapy with antidepressants. An additional problem is that some studies used a cross-over design, with the inherent risk of carry-over effects.

In a study by Goff et al. (1999 a), 50 mg/day D-cycloserine, a partial agonist at the glycine modulatory site of the glutamatergic NMDA, was tested in 47 schizophrenic patients with a deficit syndrome in a randomised, placebo-controlled trial. D-cycloserine was added to the ongoing treatment with a conventional neuroleptic for an 8-week period. Thirty-nine patients completed the trial, seven drop-outs occurred in the D-cycloserine group and only one in the placebo group. The mean reduction in negative symptoms with D-cycloserine (23 %) was significantly greater than with placebo (7 %) in the SANS. No differences were found in performance on any cognitive test between groups or in changes in any other clinical measure.

In a similar study, 100 mg/day D-cycloserine was added to typical antipsychotics in chronic schizophrenic patients with prominent negative symptoms, using a placebo-controlled, double-blind design. D-cycloserine slightly worsened the psychotic symptoms and general psychopathology as compared to placebo, and failed to change negative symptoms (van Berckel et al. 1999). The authors explained the negative result of the study by a possible antagonistic effect of this 100 mg dose of D-cycloserine at the glycine recognition site of the NMDA receptor due to competition with the endogenous agonist glycine. As another explanation for the increase in psychopathology, they suggested an interaction with the effects of antipsychotics on NMDA-mediated neurotransmission.

In another study, 50 mg/day D-cycloserine was added to ongoing clozapine treatment in schizophrenic patients with negative symptoms, using a placebo-controlled, cross-over design. D-cycloserine significantly worsened ratings of negative symptoms compared to placebo, but did not significantly affect ratings of psychotic symptoms (Goff et al. 1999 b). The authors explain the different effects of D-cycloserine on negative symptoms when added to clozapine compared to conventional antipsychotics by the assumption that activation of the glycine recognition site may play a role in clozapine's efficacy for negative symptoms.

Tsai et al. (1999) investigated in a 6-week, double-blind trial with 20 schizophrenic patients D-serine in addition to clozapine. The patients exhibited no improvement with D-serine (30 mg/kg per day) nor did their symptoms worsen.

Heresco-Levy et al. (2002) treated 24 patients in a double-blind, placebo-controlled, 6-week cross-over trial with D-cycloserine, 50 mg/day, added to the fixed antipsychotic medication. A significant reduction of negative symptoms in the D-cycloserine group was reached. The degree of improvement did not differ significantly between patients treated with conventional neuroleptics and those treated with olanzapine or risperidone.

In other studies, glycine, a non-essential amino acid that functions as an obligatory coagonist at NMDA receptors, was investigated. Heresco-Levy et al. (1999) studied 22 treatment-resistant schizophrenic patients in a double-blind, placebo-controlled, 6-week crossover trial with 0.8 g/kg per day of glycine added to their ongoing antipsychotic medication. Glycine treatment resulted in a significant reduction of negative symptoms (about 30 %) as well as an improvement in the BPRS total score. The improvement in negative symptoms was unrelated to alterations in extrapyramidal effects or

symptoms of depression. Low pre-treatment glycine serum levels significantly (r = 0.80) predicted clinical response.

In a placebo-controlled, double-blind study, glycine 60 g/day was tested as an adjunctive treatment to clozapine in 30 schizophrenic patients over eight weeks. Comedication with glycine and clozapine produced no statistically significant change in negative or positive symptoms, or cognitive functioning (Evins et al. 2000). The authors concluded that glutamatergic agents may be less effective when combined with clozapine than when combined with conventional antipsychotics.

Similarly, in a double-blind, 12-week trial on 19 treatment-resistant schizophrenic patients, Potkin et al. (1999 d) found no effects of augmentation with glycine (30 g/day) to the ongoing clozapine treatment (400–1200 mg/day). In contrast, the patients treated with clozapine without glycine had a 35 % reduction in positive symptoms.

Piracetam, a nootropic used in the treatment of organic brain dysfunction which modulates the glutamate receptor, among others, positively, was also tested in this context. Piracetam was administered as an add-on therapy to 30 mg/day haloperidol at a dose of 3200 mg/day in a placebo-controlled, double-blind study (Noorbala et al. 1999). Although both groups significantly improved in all dimensions of the PANSS scale, the combination of haloperidol and piracetam showed a significant superiority over the mono therapy with haloperidol in terms of both positive and negative symptoms.

To summarise, with respect to other experimental drugs in this field, glutamatergic agents seem an interesting tool in the treatment of negative symptoms. However, the data are quite inconsistent. There are some hints that glutamatergic agents like D-cycloserine or glycine are effective in the treatment of negative symptoms when co-administered to an ongoing treatment with classical neuroleptics. In contrast, when added to clozapine, mostly negative results were reported. The respective position concerning novel antipsychotics has not yet been sufficiently investigated. The possibility of inducing positive symptoms as a consequence of a higher dosage of D-cycloserine has to be taken into consideration.

Oestrogen as a potential treatment for schizophrenia

Oestrogen has been shown in animal studies to modulate both the dopamine and serotonin neurotransmitter systems, the main neurotransmitters implicated in the pathogenesis of schizophrenia (Kulkarni et al. 2001). Oestrogen is hypothesised to be protective for women against the early onset of psychotic symptoms of schizophrenia (Hafner et al. 1991; Seeman and Lang 1990). This "oestrogen hypothesis" was derived from epidemiological, clinical and animal studies. Epidemiological studies (Hafner et al. 1993) have shown that women with schizophrenia present with first-episode psychosis, on average, about five years later than men with schizophrenia. Life-cycle studies have also shown that women are more vulnerable for either a first episode of psychosis or relapse of an existing illness at two major periods of hormonal change: firstly during the postpartum period and secondly during the menopause (Seeman 1996). There have also been reports of women whose schizophrenic symptoms were exacerbated at low oestrogen phases of the menstrual cycle (Endo et al. 1978), and of women whose psychotic symptoms improved during the high oestrogen phase of their menstrual cycle (Riecher-Rossler et al. 1994). These clinical findings fit well with animal studies in which oestrogen has been shown to reduce the dopamine concentration in the striatum and modulate sensitivity as well as the number of dopamine receptors (Di Paolo et al. 1981; Foreman and Porter 1980). It has also been shown that oestrogen can modulate serotonin systems by increasing the expression of genes for the $5HT_{2A}$ receptor and the serotonin transporter (Sumner and Fink 1998).

Kulkarni et al. (2001) conducted a study on schizophrenic women of child-bearing age who received standardised antipsychotic medication plus 50 mcg or 100 mcg transdermal oestradiol or placebo. The results showed that women receiving 100 mcg oestradiol made greater improvements in the symptoms of schizophrenia than both the 50 mcg oestradiol or the placebo group. The significantly positive results were seen in changes in the PANSS total score, the PANSS positive score, the PANSS negative score and the PANSS general psychopathology score. Similar studies are currently being performed in this field.

Add-on therapy with oestrogens appears to be a meaningful approach and should be investigated more intensively.

Other drugs

Beta-adrenergic receptor antagonists (beta-blockers) have also been suggested as an add-on treatment in schizophrenia, especially treatment-resistant schizophrenia. Although five small placebo-controlled studies have been performed, it is difficult to draw any clear conclusions from them (Cheine et al. 2000) because the data are poorly presented and there is no evidence of any effect of beta-blockers as an adjunctive treatment (Wahlbeck et al. 2000).

Only very preliminary findings exist regarding add-on therapy with lithium in schizophrenia, with the exception of acute schizoaffective psychoses. These preliminary findings indicate that negative symptoms rarely improve and, if improvements are seen, it is only in terms of the anxiety-depression spectrum of symptoms (Schexnayder et al. 1995; Terao et al. 1995).

Recent findings suggest that a chronic over-release of 2-arachidonoyl-glycerol (2-AG), a highly lipophilic cannabinoid molecule, may be a causal factor of the cog-

nitive deficits associated with negative symptoms with schizophrenia (Pryor 2000). Drugs related to the cannabinoid systems are in development and might give a future perspective for the treatment of negative symptoms.

Conclusions

Reviews of the results of controlled studies on the efficacy of the new/atypical neuroleptics in treating negative symptoms show that in general these antipsychotics have a better effect than the classical neuroleptics on the negative symptoms of acute schizophrenic patients. However, the advantages of novel or atypical neuroleptics in negative symptoms as compared to classical neuroleptics are generally limited and often not satisfying in individual patients. Therefore it is necessary to look for alternative or additional drug treatment possibilities.

As to antidepressants in negative symptoms of schizophrenic patients, there are some positive results, especially for some serotonergic antidepressants. The clear positive results of some of these trials indicate that especially fluoxetine, fluvoxamine and also mirtazapine (only one study) might be meaningful adjunctive treatments for patients with negative symptoms. It is important to consider the potential risk of the adjunctive therapy with respect to pharmacodynamic or pharmacokinetic interaction. As to the selective serotonin reuptake inhibitors, the possible increase of neuroleptic serum levels should be carefully considered. Also, a certain risk of developing extrapyramidal symptoms (Lock et al. 1990; Meltzer et al. 1979; Tate 1989), due to the putative potentiating inhibitory effects of serotonin on nigrostriatal dopaminergic systems (Baldessarini and Marsh 1990; Tate 1989), should be anticipated.

So far anticonvulsants could not demonstrate efficacy in the treatment of negative symptoms.

With respect to other experimental drugs in this field, glutamatergic agents seem an interesting tool in the treatment of negative symptoms. However, the data are quite inconsistent. There are some hints that glutamatergic agents like D-cycloserine or glycine are effective in the treatment of negative symptoms when co-administered to an ongoing treatment with classical neuroleptics. In contrast, when added to clozapine, mostly negative results were reported. The respective position concerning novel antipsychotics has not yet been sufficiently investigated. The possibility of inducing positive symptoms as a consequence of a higher dosage of D-cycloserine has to be taken into consideration.

Add-on therapy with oestrogens seems to be a meaningful approach and should be investigated more intensively.

Other comedication strategies such as beta-blockers and lithium cannot be generally recommended due to the lack of convincing data.

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