Psychiatria Danubina, 2016; Vol. 28, No. 4, pp 435-440 *Conference paper*

THE RELEVANCE OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA AND HOW TO TREAT THEM WITH PSYCHOPHARMACEUTICALS?

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SUMMARY

Negative symptoms are highly prevalent in the acute episode and long-term course of schizophrenia. They are often persistent and tend to chronicity. They have an important negative impact on different dimensions of outcome and therefore require careful diagnosis and treatment. However, the evidence for the available psychopharmacological treatments is still not satisfactory and further research is needed.

Antipsychotics, especially some second-generation antipsychotics, are the primary treatment of choice, particularly for negative symptoms in the acute episode. In case of residual negative symptoms concomitant treatment with antidepressants is often indicated. Glutamatergic compounds are of great theoretical interest as an add-on treatment or even as a monotherapy, but so far the efficacy results are inconsistent and their clinical use is limited.

Key words: *negative symptoms – schizophrenia – antipsychotics – antidepressants - glutamatergic compounds*

ZUSAMMENFASSUNG

Die Negativsymptomatik hat eine hohe Prävalenz sowohl in der akuten Episode als auch im langfristigen Verlauf der Schizophrenie. Sie ist oft persistierend und neigt zur Chronifizierung. Sie hat wichtige negative Auswirkungen auf die verschiedenen Dimensionen des Krankheitsausgangs und erfordert daher eine sorgfältige Diagnose und Behandlung. Die Evidenzlage für die verfügbaren psychopharmakologischen Behandlungen ist jedoch noch nicht zufriedenstellend und weitere Forschung ist notwendig.

Antipsychotika, vor allem einige Antipsychotika der zweiten Generation, sind die bevorzugte Behandlung der Wahl, vor allem bei der Negativsymptomatik der akuten Episode. Bei einem schizophrenen Residuum ist eine gleichzeitige Behandlung mit Antidepressiva oft angezeigt. Glutamaterge Präparate sind von großem theoretischen Interesse als Add-on-Behandlung oder sogar als Monotherapie, aber die Wirksamkeitsergebnisse sind bisher inkonsistent und ihre klinische Anwendung ist begrenzt.

Schlüsselwörter: *Negativsymptomatik – Schizophrenie – Antipsychotika – Antidepressiva - glutamaterge Präparate*

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INTRODUCTION

Negative symptoms are associated with detrimental effects on patients' functional status, quality of life and long-term outcome. Their clinical expression is less obvious than that of positive symptoms, because they can be masked by positive symptoms and can coexist with or be confused with affective symptoms or cognitive impairment (Moller 2007).

Negative symptoms are most frequently associated with schizophrenia, but clinically similar disturbances may also occur in patients with other psychiatric disorders (Moller 2007). The negative symptoms of schizophrenia are classified as primary or secondary. Primary negative symptoms are a core feature intrinsic to schizophrenia itself, whereas secondary negative symptoms are transient and are attributable and temporally related to such factors as unrelieved positive symptoms, adverse effects of antipsychotic drugs, or the social isolation resulting from schizophrenia, and they often subside with resolution of the causative factors (Carpenter et al. 1988). Even though primary and secondary negative symptoms have different aetiologies, their clinical expression is similar.

Negative symptoms are referred to as "persistent negative symptoms" if they have been present for a predefined period, most commonly specified as 6 or more months (Buchanan 2007), or as a "deficit syndrome" if they have been present for longer than 12 months (Buchanan 2007, Kirkpatrick et al. 1989). Referring to negative symptoms as persistent negative symptoms or a deficit syndrome implies that they are a primary phenomenon and are not explainable by side effects of neuroleptics, depression, social withdrawal, etc. However, secondary negative symptoms can be persistent if the causative factors remain unresolved for the defined time period. Persistent negative symptoms are more common in schizophrenia than in depressive disorders (Bottlender et al. 2003). The clinical impact of negative symptoms, measured as poorer outcome, appears to be greater in schizophrenia than in affective or schizoaffective psychosis (Moller et al. 2000).

Negative symptoms can have a significant impact on clinical and functional outcomes (Bottlender et al. 2010, Moller et al. 2010). For example, apathy can reduce compliance, which tends to be poor in general among patients with schizophrenia. Furthermore, poor compliance with drug treatment is a main contributor to the risk of relapse. In addition, several studies have found that negative symptoms correlate significantly with decreased quality of life (Bow-Thomas et al. 1999, Fitzgerald et al. 2003, Fitzgerald et al. 2001, Rudnick & Kravetz 2001), although one study found contradictory results (Delamillieure et al. 2005).

This paper addresses the issue of negative symptoms as residual symptoms and the current evidence for psychopharmacological treatment of negative symptoms. It is based on my group's study on residual symptoms in schizophrenia (Schennach et al. 2015) and my recent review on the psychopharmacological treatment of negative symptoms (Moller & Czobor 2015).

THE PREVALENCE AND IMPORTANCE OF NEGATIVE SYMPTOMS AS RESIDUAL SYMPTOMS

In a prospective 1-year follow-up study Schennach et al. (2015) investigated among other things the prevalence of negative symptoms at admission to and discharge from the index hospitalisation and at the 1-year follow-up and thereby focussed on the aspect of residual symptoms. The original sample consisted of 399 patients with a diagnosis of schizophrenia or a schizophrenia spectrum disorder according to DSM-IV. Schizophrenia-related psychopathological symptoms were assessed with the PANSS.

At discharge 236 patients had achieved remission defined according to the consensus criteria for remission (Andreasen et al. 2005). Of these patients, only 6% were complete remitters without any residual symptoms. A total of 94% of the remitters had at least one residual symptom, 86% had two, 77% had three, and 69% had four or more. A comparison of the PANSS total score between the non-residual and residual remitters showed that remitters without residual symptoms at discharge had presented significantly fewer psychopathological symptoms starting from treatment week 2 ($p<0.0001$). The ten most common residual symptoms in patients who met the remission criteria at discharge were as follows (in declining order): blunted affect (49%), conceptual disorganization (42%), passive/apathetic social withdrawal (40%), emotional withdrawal (39 %), lack of judgment and insight (38%), poor attention (36%), somatic concern (34%), difficulty in abstract thinking (33%), anxiety (33%) and poor rapport (33%) (Schennach et al. 2015).

To analyse whether residual symptoms are associated with tolerability, overall functioning and long-term outcome, Schennach et al. (2015) compared different clinical variables (sociodemographic and illness-related variables, Global Assessment of Functioning (GAF), UKU Side Effect Rating Scale (UKU) total score, remission at the one-year follow-up assessment, relapse within the one-year follow-up) between remitted patients with and without residual symptoms. They found no significant correlation between residual symptoms and age ($p=0.7065$), gender ($p=0.7891$), diagnostic subtype ($p=0.7065$), number of illness episodes ($p=1$) or the level of comorbidity ($p=1$). The non-residual remitters had significantly fewer side effects (non-residual group: UKU total mean score 0.79 (SD 1.05); residual group: UKU total mean score 5.67 (SD 5.46); $p<0.0001$) at discharge and significantly greater functioning (non-residual group: GAF mean score 79.71 (SD 7.97); residual group: GAF mean score 69.55 (SD 10.97)). Furthermore, remitted patients with no residual symptoms at discharge were more likely to achieve remission and have fewer relapses than patients with residual symptoms, although the difference was not statistically significant (remission at follow-up: non-residual group 80% chance, residual group 71% chance; relapse: non-residual group 30% chance, residual group 47% chance).

To estimate the endurance and persistence of residual symptoms, Schennach et al. (2015) evaluated the symptomatic status of patients one year after discharge. Of the 236 patients in remission at discharge, 133 patients were available for follow-up and 94 patients fulfilled remission criteria at both discharge and one-year follow-up. The most prevalent residual symptoms in this subgroup at follow-up were blunted affect (37%), social withdrawal (28%), emotional withdrawal (27%) and anxiety (27%). Interestingly, about one-third to one-half of all patients with a particular residual symptom at discharge still showed the same symptom at follow-up; the most common such symptoms were blunted affect (50%), difficulty in abstract thinking (44%) and social withdrawal (41%).

To my knowledge, Schennach et al. (2015) was the first study to evaluate persisting symptoms in remitted schizophrenia patients at discharge. The study found residual symptoms in 94% of remitted patients, the most common of which were blunted affect, conceptual disorder and social withdrawal. Residual symptoms at discharge were found to be associated with the level of functioning and with the risk of relapse and chance of remission at follow-up. The results highlight the need to evaluate and treat residual symptoms in remitted patients, given their impact on outcome.

EVIDENCE FOR THE EFFICACY OF PSYCHOPHARMACOLOGICAL TREATMENT OF NEGATIVE SYMPTOMS

Despite intensive research activities the neurobiological background of negative symptoms is still not completely clear (Galderisi et al. 2015). Several hypotheses are of interest, including those on structural and functional brain alteration, transmitter alterations in the dopaminergic, serotonergic and glutamatergic systems and genetic predispositions, but so far only the glutamate hypothesis has led to the development of new compounds.

As described in detail in my recent review paper on this issue (Moller & Czobor 2015) many clinical studies do not pay attention to a variety of methodological problems associated with the evaluation of psychopharmacological treatment of negative symptoms in schizophrenia. Among other aspects the measurement of negative symptoms needs to be improved (Garcia-Portilla et al. 2015).

The following presents a summary of the findings of the above mentioned review (Moller & Czobor 2015). The review considered in particular three meta-analyses on the efficacy of antipsychotics by Leucht et al. (Leucht et al. 2009a, Leucht et al. 2009b, Leucht et al. 2009c) and found the results to be somewhat ambiguous and inconsistent. The initial hope after the introduction of the SGAs that they would be superior to FGAs was not at all confirmed and only four SGAs (amisulpride, clozapine, olanzapine and risperidone) were found to show better efficacy in general than FGAs. Nevertheless, most of the above mentioned meta-analyses showed that second-generation antipsychotics (SGAs) and first-generation antipsychotics (FGAs) have some efficacy in negative symptoms when compared with placebo (Leucht et al. 2009a, Leucht et al. 2009b, Leucht et al. 2009c). The results of the three meta-analyses by Leucht et al. (Leucht et al. 2009a, Leucht et al. 2009b, Leucht et al. 2009c) mirror to a certain extent the results of an earlier meta-analysis by the same group (Leucht et al. 1999). This meta-analysis only evaluated the SGAs olanzapine, quetiapine, risperidone and sertindole and found that risperidone and olanzapine are somewhat superior to haloperidol in reducing negative symptoms. An explanation for the slightly disappointing results might be that the majority of studies were performed in patients with acute episodes and predominant positive symptoms (Moller & Czobor 2015).

Antidepressants are the most widely used comedication for negative symptoms in schizophrenia, although the evidence for their efficacy is limited (Moller & Czobor 2015). A review and meta-analysis of add-on treatment with antidepressants by Singh et al. (2010) included 23 studies (22 publications, total N=819) of selective serotonin reuptake inhibitors (SSRIs), mirtazapine, reboxetine, mianserin, trazodone and ritanserin that applied certain predefined criteria regarding randomisation, blind assessment, placebo control of the add-on treatment, standardised rating scales and illness chronicity (illness duration more than 2 years). The overall standardised mean difference (SMD) was -0.48, which the authors considered to be moderate. Subgroup analyses found significant responses for fluoxetine, trazodone and ritanserin. The systematic review and meta-analysis by Singh et al. (2010) supports the view that treatment with antidepressants as an add-on to antipsychotic treatment is more effective in negative symptoms of schizophrenia than treatment with antipsychotics alone.

The recently published meta-analysis by Kishi and Iwata (2014) considered add-on studies with mianserin and mirtazapine, both of which were classified as 'noradrenergic and specific serotonergic antidepressants'. The analysis included 12 studies (seven on mirtazapine, N=221; five on mianserin, N=141; total N=362). Add-on treatment with one of the two antidepressants was found to be superior to placebo in improving negative symptoms (SMD=-0.88; 95% CI -1.41 to -0.34, p=0.001) and overall symptom severity. No significant difference as regards improving positive symptoms or depressive symptoms.

In their recent meta-analysis Hecht & Landy (2012) evaluated add-on therapy with alpha-2 receptor antagonists (mostly mirtazapine and mianserin) in schizophrenia. When administered in addition to a D2 antagonist, a presynaptic alpha-2 receptor antagonist can cause an efflux of dopamine in the frontal cortex; this effect is hypothesised to be helpful in treating negative symptoms and cognitive impairments. The meta-analysis identified and included eight studies, each of which had a sample size of 18-41 patients and administered treatment for 4-8 weeks. The overall effect size, expressed as SMD, was 0.84 for negative symptoms (95% CI 0.17-1.51) and 0.16 (95% CI 0.30-0.62) and -0.88 (95% CI 0.15–1.46) for symptoms overall. Five studies examined improvements in negative symptoms and depressive symptoms (measured with the Hamilton Depression Rating Scale) and three of these five found significant improvements in the former but no change in the latter. The authors suggested performing a more definitive clinical trial to confirm the positive effects of alpha-2 antagonists (Hecht & Landy 2012).

In recent years the glutamate hypothesis of schizophrenia (Kantrowitz & Javitt 2010) has become the most feasible neurobiological theory of schizophrenia to explain both positive and negative symptoms. Although naturally occurring glutamatergic compounds had already been investigated for several years in smaller proof-of-concept trials, glutamatergic compounds are currently of great interest for the development of drugs for schizophrenia, either for the disorder as a whole or for negative or cognitive symptoms in particular (Lopez-Munoz & Alamo 2011). A principal issue with all these compounds is avoiding an overactivation of the glutamatergic system. The most promising and most studied mechanisms include agonists at the glycine-binding modulatory site of the N-methyl-d-aspartate (NMDA) receptor, glycine transporter inhibitors, modulators of the AMPA receptor and selective agonists of the metabotropic receptor Glu2. Most of the compounds available for the treatment of negative symptoms are NMDA antagonists. The following compounds have been studied somewhat more closely, although most of the studies were small and short term (Palmquist 2011): glycine (a naturally occurring amino acid; full agonist at the glycine modulatory site of the NMDA receptor), d-serine (a naturally occurring amino acid; full agonist at the glycine modulatory site of the NMDA receptor), d-cycloserine (antituberculosis medication; partial agonist at the glycine site of the NMDA receptor) and sarcosine (a naturally occurring amino acid; glycine transporter inhibitor with low affinity). Most of the efficacy studies evaluated the respective compound as an add-on to antipsychotic treatment and thus focused primarily on somewhat persistent negative symptoms. Most of the study samples were small or very small so that the studies were often underpowered, which is important to

remember when evaluating the results. Some studies with glycine, d-serine, d-cycloserine or sarcosine found an improvement in negative symptoms, which was sometimes accompanied by an improvement in cognitive and positive symptoms. However, the findings of other studies were negative, especially when clozapine was the antipsychotic (Coyle & Tsai 2004, Duncan et al. 2004, Evins et al. 2000, Goff et al. 2008, Heresco-Levy & Javitt 2004, Heresco-Levy et al. 1996, Javitt 2010, Javitt et al. 2001, Thomas et al. 2014). The referenced studies are given as examples and cannot be described here in more detail because of space limitations.

One Cochrane review and meta-analysis (Tuominen et al. 2006) examined randomised control-group studies identified in the Cochrane Schizophrenia Group's Trials Register between May 2002 and October 2003. Eighteen trials were included on the basis of predefined criteria, all of which were small (N=6 and 51; total N=358). All of the studies were short term (maximum duration 12 weeks) and used glycine, d-serine, d-cycloserine or ampakine CX 516 as an add-on to antipsychotic treatment. d-cycloserine had no effect on the symptoms of schizophrenia, whereas glycine and d-serine showed some efficacy in reducing negative symptoms (N=132, SMD -0.66, CI -1.0 to -0.3, p=0.0004), although the magnitude of the effects was moderate. Furthermore, the data for responder rates as regards negative symptoms were inconsistent: responder rates (>20% improvement in negative symptoms) for glycine and controls did not differ (N=62, RR 0.70, 95% CI 0.3-1.71) and glycine only showed a tendency towards superiority as regards >50% improvement (N=62, RR 0.87, 95% CI 0.8-1.00). The rating scale data on positive symptoms and cognitive functioning did not indicate statistically significant effects of glycine or d-serine. The authors summarised that glycine and d-serine as add-on treatment to regular antipsychotic medication may improve negative symptoms somewhat, but that the results are not fully consistent and the database is too small to draw any firm conclusions (Moller & Czobor 2015).

Recently pharmaceutical companies have developed new pharmacological compounds that affect the glutamatergic system (Arango et al. 2013). Two of them are worth mentioning here because findings in the first clinical phase II studies were positive: bitopertin and Ly 404039. Bitopertin is a glycine transporter antagonist, developed by Roche, that showed efficacy in treating negative symptoms as an add-on to antipsychotics in a phase II study (Umbricht et al. 2014). However, the negative findings of two later phase III studies (Thomas et al. 2014) resulted in Roche discontinuing further development of bitopertin in this indication. Ly 404039 is a selective agonist for the mGlu2/3 receptor, developed by Lilly, that in a monotherapy phase II study showed efficacy in treating both positive and negative symptoms (Patil et al. 2007); subsequent studies, however, were negative. Arango et al. (2013) give an overview of other compounds currently being studied.

GENERAL CONCLUSIONS

Satisfactory treatment of negative symptoms is one of the most important unmet needs in the treatment of schizophrenic disorders. The evidence for current psychopharmacological treatments is difficult to evaluate because of methodological problems and inconsistent results. As a consequence definite, empirically based conclusions are difficult to reach and any such conclusions should be considered with great caution.

Generally speaking, SGAs do not appear to be as effective as anticipated in the treatment of negative symptoms, although some of them are apparently more effective than FGAs in the treatment of symptoms in general and some in negative symptoms (Moller & Czobor 2015). The findings in negative symptoms, however, are mainly during an acute episode of schizophrenia, i.e. the negative symptoms are presumably secondary to positive symptoms. Studies specifically on predominant persistent negative symptoms are rare and only a very few SGAs have been evaluated in this indication, for example amisulpride, which showed some efficacy.

Because of the unclear efficacy of SGAs, clinicians often administer add-on treatment to antipsychotics, particularly for somewhat persistent negative symptoms. Add-on treatment with antidepressants, for example, is common and this approach has been evaluated in several studies, mostly with modern antidepressants such as the SSRIs, selective dual action antidepressants and alpha-2 receptor blocking antidepressants, although samples were relatively small. Taken together the empirical results provide some evidence for efficacy of such combined treatment.

Several studies, again with small samples, have evaluated add-on treatment with glutamatergic compounds, e.g. the naturally occurring amino acids glycine or d-serine or the newly developed pharmacological compounds. Although the findings are highly inconsistent, overall they appear to indicate positive effects. A very important issue in the pharmacological treatment of schizophrenic disorders is the avoidance of inducing secondary negative symptoms, e.g. due to parkinsonian side effects. In this regard SGAs, which have a low risk of extrapyramidal side effects, have some advantages.

Acknowledgements:

The author thanks Jacquie Klesing, Board-certified Editor in the Life Sciences (ELS), for editing assistance with the manuscript.

Conflict of interest: None to declare.

In the recent years the author has received honoraria for his services as a consultant or speaker from the following pharmaceutical companies: Lundbeck, Lilly, Otsuka, Servier, Schwabe.

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