

RESPONSE AND REMISSION IN SCHIZOPHRENIA: THE LIMITED VALUE OF NEW REMISSION CRITERIA

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Abstract

Object: The Remission in Schizophrenia Working Group proposed in 2005 criteria for remission in patients with schizophrenia. This composite criterion consists of eight PANSS items and is reached when none of those has a score of more than 3 during a period of 6 months. The present study was done to elucidate the clinical relevance of this concept.

Method: A group of 65 patients with schizophrenia was treated with atypical antipsychotics for 14 weeks. At baseline and endpoint, severity of symptoms was assessed with the PANSS, the BPRS, a cognitive subscale derived from the PANSS, and the CGI. A reduction of at least 50% on the BPRS total score was considered to be clinically relevant.

Results: At endpoint, 18 patients (28%) had a reduction of 50% or more on the BPRS and 25 patients (39%) reached the severity criterion of remission. No correlation was found between the summed scores of the remission items and those of the cognitive subscale. Remitters and non-remitters did not differ with respect to the total score on the cognitive subscale. Predictors for remission were the PANSS positive and negative sum scores and age. Remission was reached by an only marginal symptomatic improvement.

Conclusions: In this patient group, remitters are still symptomatically (e.g. cognitively) impaired and definitely not recovered, which implies that the term remission should be better replaced by partial symptomatic remission.

Key Words: Schizophrenia – Remission – Symptom – Atypical Antipsychotics – Cognitive Function

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Introduction

For more than a century, clinical course and outcome of schizophrenia have been the subject of scientific discussion. As reviewed by Hegarty et al. (1994), the results are highly variable depending both on the used diagnostic criteria, and on the variety of criteria to express outcome. Shortly after the introduction of the antipsychotics in the fifties of the last century, standardized criteria for diagnosis and treatment efficacy have been developed. The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) that was subsequently included in the Positive and Negative Syndrome Scale for Schizophrenia

(PANSS; Kay et al. 1988), became the golden standard. From that time, treatment response was defined as the percentage reduction of the total BPRS score. Since symptom reduction as such did not satisfy clinical assessment, the Clinical Global Impression Scales (CGI; Guy 1976) were introduced to assess illness severity and improvement.

Factor analytical studies of the PANSS have established cognitive disorganization as a domain separate from positive and negative symptoms (Lepine et al. 1989). As reviewed by Bryson et al. (1999), this cognitive dimension that was demonstrated by Bell et al. (1994), shows concurrent validity with established neuropsychological measures. Poor insight of the

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patient in the presence of a mental disorder, has been demonstrated to be associated not only with medication adherence but it also an independent factor that has a predictive value for outcome (Lincoln et al. 2007, Emsley et al. 2008). In addition, it has been proposed that impaired functioning of the prefrontal cortex in schizophrenia is associated with impaired insight (Aleman et al. 2006). Symptomatic improvement in positive and negative symptoms alone, does not automatically imply amelioration of cognitive impairment.

The introduction of clozapine in 1990 and its licensing for treatment resistant schizophrenia, necessitated a clear definition of treatment resistance and as a consequence, of treatment response. Kane et al. (1988) were the first to present criteria derived from clinical history and BPRS scores. Subsequently, Meltzer et al. (1998) stated that treatment responsiveness should include not only a symptomatic improvement but also improvement on several other outcome criteria. The latter was further elaborated by Peuskens (1999) who listed outcome measures relevant in schizophrenia, e.g.: cognitive functioning, interpersonal social function, treatment compliance and service utilization. The Cochrane database pays tribute to this development, in that an array of outcome measures is used in the systematic reviews (Verhoeven et al. 2005). The importance of a critical use of the outcome criteria in research on the effectiveness of antipsychotics, is illustrated by the long term and independent CutLass I and CATIE studies which demonstrate that the presumed benefits of novel antipsychotics are not reflected in either treatment adherence (Lieberman et al. 2005) or quality of life, symptoms and costs (Jones et al. 2006) or cognitive function (Keefe et al. 2007). In addition, the so called MATRICS initiative acknowledges that cognitive dysfunctions are core symptoms of schizophrenia that occur rather independent of psychotic symptoms and are the most relevant for prognosis (Green et al. 2004, Bromley 2005). As underlined by Stip (2006) cognitive deficits should be included in the assessment of patients with schizophrenia in clinical practice because of their predictive value for social adaptation. The latter was demonstrated in a long term study by Carlsson et al. (2005), who found that cognitive functioning at admission predicted outcome better than symptoms or diagnosis in patients with a first episode psychosis. Similar findings were reported by Helldin et al. (2006).

Over the past decades, several predefined criteria for symptomatic remission have been proposed that all include positive and negative psychotic symptoms whereas some use also assessment of global functioning. The time frame varies from a single time point evaluation to several years. In patients with acute symptoms, improvement covers mostly a period of 8 weeks (Leucht and Lasser 2006). For chronic populations, Lieberman et al. (2002) suggested to delineate symptom remission as part of an operational definition of recovery, which consists of a score of 4 or less (moderate) on each of the positive and negative symptom items of the BPRS for two consecutive years. Subsequently, Lieberman et al. (2003) proposed for acute populations an a priori response criterion of 50% reduction on the BPRS total score with no score greater

than 3 (mild) on either of the five BPRS psychosis items (unusual thought content, suspiciousness, hallucinations, conceptual disorganization, mannerisms and posturing) and a CGI severity score of mild (3 or less) without a time frame. In first episode schizophrenia, Robinson et al. (2004) defined symptomatic remission as a rating of no worse than mild on 6 positive symptom items together with a score of no worse than moderate on 4 negative symptom items for two consecutive years.

Andreasen et al. (2005) chose to focus on symptomatic remission only, since they considered that there is no adequate knowledge base as yet for the long term course of cognitive and psychosocial outcomes and their relationship to changes in severity and pattern of symptoms in schizophrenia. The Remission in Schizophrenia Working Group defined remission as a mild or less score for 8 items from the PANSS for a period of at least 6 months leading to a state in which patients have symptoms of such a low intensity that they do not interfere significantly with behaviour. These items are derived from the three dimensions that emerge from factor analytical studies with the PANSS (Arndt et al. 1995). As stated by Gorwood (2005) this endeavour can be regarded as an operationalization of the DSM-IV specifier 'remission'. Although remission should be read as symptomatic remission, the ambition of this concept is much higher since the underlying assumption is that with remission there are no appreciable effects on daily functioning or subjective well-being left (Remington and Kapur 2005).

In the present study symptomatic improvement after 14 weeks in a group of patients with relapsing schizophrenia was studied by comparing this remission criterion with a priori defined BPRS response criterion.

Material and Methods

Subjects:

Male and female patients with schizophrenia were included if they were at least 18 years of age and suffered from an acute episode, a relapse after a

Table 1. *Main characteristics of the patients (n=65)*

<i>Schizophrenia subtypes (DSM-IV)</i>	
-295.1 disorganized	13
-295.2 catatonic	2
-295.3 paranoid	38
-295.9 undifferentiated	12
<i>Male/Female</i>	40/25
<i>Age ± SD</i>	26.2 ± 10.4
<i>Duration of illness* ± SD</i>	6.4 ± 7.3
<i>Treatment regimens</i>	
Risperidone	22
Olanzapine	15
Sertindole	7
Quetiapine	13
Aripiprazole	8

* Time since onset of psychotic symptoms

symptom-free interval or an exacerbation of chronic illness. All met the DSM-IV criteria for schizophrenia and were inpatients of a psychiatric hospital. Patients were excluded if they had a diagnosis of DSM-IV organic mental disorder or substance abuse disorder, serious unstable somatic disease(s) and a history of seizures or clinically relevant laboratory abnormalities. The main characteristics of the patients including subclassification according to the DSM-IV and duration of illness are presented in table 1. The study followed an open baseline controlled design and was conducted in full accordance with the Helsinki principles.

Treatment protocol:

The atypical antipsychotics risperidone (R), olanzapine (O), sertindole (S), quetiapine (Q) and aripiprazole (A) were administered as part of an ongoing research project on the clinical effectiveness of these compounds. Treatment started after a washout and screening period of 2 to 9 days. The treatment period lasted 14 weeks. The initial daily doses for R, O, S Q and A were 2, 10, 4, 25 and 15 mg respectively. Dosages were subsequently titrated individually during 6 weeks to a mean daily dose at endpoint of 9.1 mg for R, 12.5 mg for O, 20 mg for S, 429 mg for Q and 15mg for A. The clinical results, except those of A, have been published elsewhere (Van der Heijden et al. 2004).

Assessment of psychopathology and remission:

The severity of psychopathology was assessed by means of PANSS and the CGI-severity. In order to optimize interrater reliability, PANSS scoring was trained at the certified course provided by the department of psychiatry of the University Medical Centre Utrecht (head: Prof. Dr. R.S. Kahn). Patients were included if the BPRS total score at baseline was at least 16. Clinically relevant improvement was defined as a 50% or more reduction of the BPRS total score at endpoint. All assessments were performed at baseline and at weeks 6 and 14 (endpoint).

Patients were considered to have reached a remission (excluding the time component) if at endpoint

(14 weeks) the scores on 8 PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganisation (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6), were 3 or less. In addition, PANSS items at face value related to cognitive function and suggested to correlate with established neuropsychological measures (Bryson et al. 1999) were summed to create the cognitive domain [PANSS-COGN; 9 items: conceptual disorganization (P2), difficulty in abstract thinking (N5), stereotyped thinking (N7), motor retardation (G7), disorientation (G10), poor attention (G11), lack of judgment and insight (G12), poor impulse control (G14) and preoccupation (G15)]. The PANSS item Lack of Judgment and Insight (nr. 26) was used as a parameter separately. Finally, the CGI-severity score was used to include a clinician-based judgment of illness severity. In addition, the remission criteria according to Lieberman et al. (2003) were applied that comprises 50% BPRS total score reduction + score < 4 on the 5 psychotic BPRS-items + CGI < 4.

Statistics

Standard paired-samples t-test was used to examine group differences. Correlation analysis was done with the Pearson-r and used to assess the relation between the sumscores on the PANSS non-remission items and the PANSS-COGN items. Stepwise discriminant analysis was applied to calculate the relative contribution of selected variables in the prediction of remission versus non-remission group membership.

Results

The study included a total of 65 patients. The scores on the rating instruments at baseline and after 6 and 14 weeks are depicted in table 2. Dispersion of PANSS variables (PANSS-POS, PANSS-NEG, PANSS-TOT, PANSS-COG, PANSS-Lack of Insight) was

Table 2. Scores ($\pm$ SD) on the rating instruments of the patients (n=65)

	Baseline	6 weeks	14 weeks
PANSS-POS ¹	19.2 $\pm$ 6.2	14.6 $\pm$ 5.3	14.2 $\pm$ 6.4
PANSS-NEG ²	24.5 $\pm$ 7.9	20.3 $\pm$ 7.0	19.4 $\pm$ 7.4
PANSS-COGN ³	25.9 $\pm$ 8.9	21.4 $\pm$ 6.9	21.0 $\pm$ 7.8
BPRS ⁴	45.7 $\pm$ 15.7	35.4 $\pm$ 15.2	32.4 $\pm$ 16.9
CGI-SEV	4.8 $\pm$ 1.1	4.0 $\pm$ 1.3	3.7 $\pm$ 1.5

¹PANSS-POS = Positive and Negative Syndrome Scale (7 item positive symptom subscale)

²PANSS-NEG = Positive and Negative Syndrome Scale (7 item negative symptom subscale)

³PANSS-COGN = Cognitive Subscale (9 items; see: Material and Methods)

⁴BPRS = Brief Psychiatric rating Scale (7 items)

examined through visual inspection of normal probability plots and calculation of Kolmogorov-Smirnov's and Shapiro-Wilk's test. Normality of all variables was acceptable both at baseline and at endpoint, except for the one-item PANSS-Lack of insight.

After 6 and 14 weeks, 5 and 18 patients, respectively, fulfilled the BPRS response criterion. At 6 weeks, 3 patients from this response group ($n=5$), reached also the remission criterion of a score of 3 or less on each of the 8 PANSS items. Of the patients who had a reduction on the BPRS total score of less than 50%, 18 were remitters. At endpoint, 18 patients were responders of whom 14 were remitters too. Of the non-responders ($n=47$), 11 met the remission criterion. These data demonstrate an overlap between the response and remission criteria of 69% (45/65) after 6 weeks and of 77% (50/65) at endpoint. According to the remission criterion of Lieberman et al., 18 patients had a remission at week 14. Data on response and remission are presented in table 3.

The baseline characteristics and the scores on the rating instruments of the group of patients that reached the remission criterion at 14 weeks versus the non-remitting group are presented in table 4.

The mean sum score of the remission items decreased from 27.7 ± 7.6 to 20.5 ± 8.1 (26%) and the mean sum score of the PANSS-items that are not included in the remission criterion, decreased from 59.7 ± 16.0 to 48.5 ± 15.0 (19%).

Table 3. Number of patients with response and remission

<i>Response/Remission</i>	<i>6 weeks(n)</i>	<i>endpoint(n)</i>
BPRS 50% reduction	5	18
Andreasen criterion	21	25
Lieberman criterion	4	18

The PANSS-COGN in the total group decreased from 25.9 ± 8.9 to 20.9 ± 7.9 (19%)

The correlation between the sumscores on the remission items and those on the COGN-items both at baseline and at endpoint appeared to be remarkably low ($r = .005$ and $.128$ respectively).

The PANSS item lack of insight decreased in the remission versus the non-remission groups from 3.2 and 4.3 to 2.3 and 4.0, whereas the PANSS-COGN decreased from 25.6 and 26.1 to 21.3 and 20.8.

With respect to the CGI-severity scores, 25 of the patients (38%) had a score of 3 or less after 6 weeks. At endpoint, 33 patients (51%) were mildly ill or less. From the total group, 21 patients met the remission criterion at 6 weeks of whom only 12 had a CGI severity score of maximum 3. At endpoint, 20 of the 25 remitters had also a CGI severity score of 3 or less. The overlap between the remission criterion and the CGI severity score at weeks 6 and 14 was 66 and 72% respectively.

Since the baseline scores on the PANSS Positive and Negative subscales and on the item Lack of Insight as well as mean age and duration of illness were significantly different in remitters versus non-remitters, discriminant analysis was performed in order to assess their relative contribution to the prediction of group membership at 14 weeks. It appeared that especially PANSS Positive and Negative scores as well as age predicted group membership with 78.5% of the cases being correctly classified. This indicates that being younger and having lower scores on the PANSS subscales are both predictive of remission-group membership.

In order to elucidate what symptomatic improvement makes a patient a remitter, the items included in the remission criterion were investigated separately. The evolution in time of the 8 remission items is depicted in figure 1. As can be inferred, remission is attained with the PANSS items delusions (P1), blunted affect (N1), social withdrawal (N4) and unusual thought content (G9), especially with delusions and unusual thought content.

Table 4. Baseline characteristics (mean $\pm$ SD) of remitters versus non-remitters after 14 weeks of treatment with atypical antipsychotics

	<i>Remitters (n=25)</i>	<i>Non-remitters (n=40)</i>
Age	23.0 ± 4.6	27.9 ± 12.5
Duration of illness	3.0 ± 2.9	8.5 ± 8.4
PANSS-POS ¹	15.4 ± 4.5	21.5 ± 6.0
PANSS-NEG ²	19.8 ± 5.7	27.5 ± 7.7
PANSS-COGN ³	25.6 ± 8.3	26.1 ± 9.3
Lack of Insight ⁴	3.2 ± 1.1	4.3 ± 1.5
BPRS ⁵	36.6 ± 9.7	51.4 ± 16.2

¹ PANSS-POS = Positive and Negative Syndrome Scale (7 item positive symptom subscale)

² PANSS-NEG = Positive and Negative Syndrome Scale (7 item negative symptom subscale)

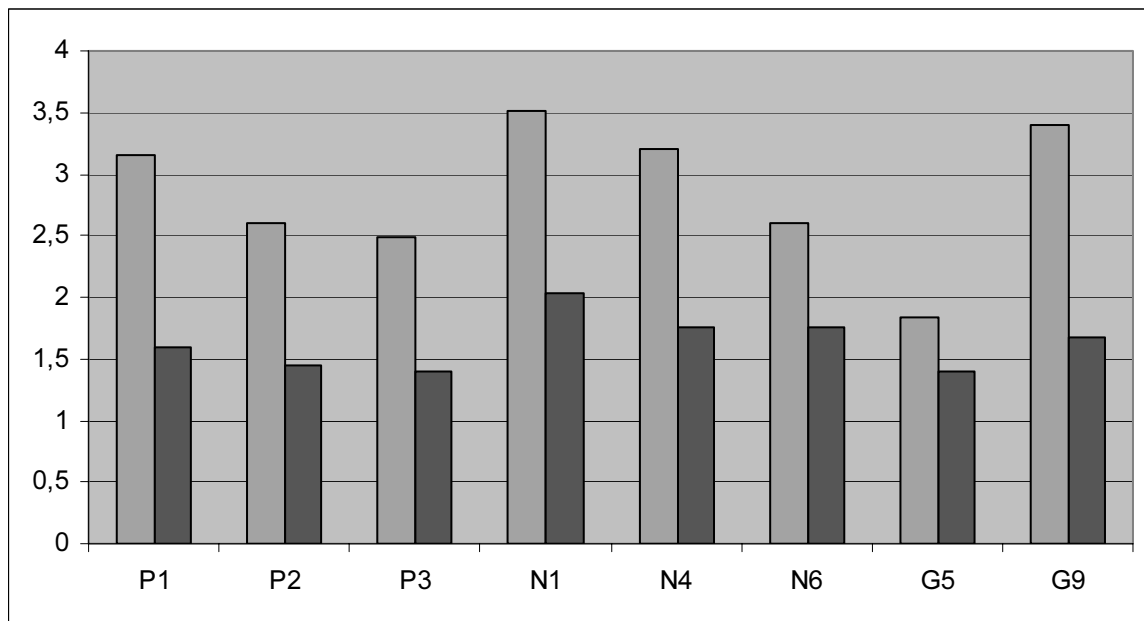
³ PANSS-COGN = Cognitive Subscale (9 items; see: Material and Methods)

⁴ PANSS item 26

⁵ BPRS = Brief Psychiatric rating Scale (7 items)

All differences are significant at the 5% level, except for PANSS-COGN and Lack of Insight

Figure 1. Baseline (first bar) versus 14 weeks (second bar) of the 8 remission items according to Andreasen et al. in patients with remission ($n=25$).



P1=Delusions, P2=Conceptual disorganisation, P3=hallucinatory behaviour N1=Blunted affect, N4=Social withdrawal, N6=Lack of spontaneity G5=Mannerisms/posturing, G9=Unusual thought content.

Discussion

The present study demonstrates that in a relatively small group of patients with schizophrenia referred for an acute episode to a clinical facility, 38,5% of the patients ($n=25$) met the remission criterion after 14 weeks of treatment with an atypical antipsychotic and that there is a considerable overlap with the BPRS response criterion of 50%. There is also a marked overlap between the remission criterion and a CGI severity value of 3 or less. With the more stringent remission criterion as proposed by Lieberman et al. (2003), however, only 18 patients (28%) were remitters.

The main parameters predictive for remission are PANSS positive and negative scores as well as age. As presented in figure 1, remission can be achieved with an only marginal reduction of half of the PANSS items included in the criterion. Furthermore, the symptomatic improvement in the total group of patients for the summed remission items, the summed remaining PANSS items and the cognitive domain items appears to be 26%, 19% and 19% respectively.

Since the severity of cognitive impairment and insight are the main predictors of functional outcome (Kopelowicz et al. 2005, Bowie and Harvey 2006, Stip 2006, Aleman et al. 2006, Shad et al. 2006, Lincoln et al. 2007, Emsley et al. 2008) and since no correlation between the summed remission items and those reflecting the cognitive domain is found, the clinical relevance of reaching the remission state can be

doubted. It should be stressed, however, that a cognitive subscale, as used in the present study, replaces by no means formal neuropsychological testing (Hofer et al. 2007). Recently, Mohamed et al. (2008) showed that neurocognition and symptom measures are independently and significantly associated with functional outcome.

The remission criterion as proposed by Andreasen et al. (2005) is conceived to describe a symptomatic level that no longer impedes daily functioning which, per definition, implies a syndromal recovery. So far, a very limited number of studies using this remission criterion has been published. Lasser et al. (2005) performed a re-analysis of the data collected in previous registration studies for long-acting risperidone and concluded that in 20% of the included non-remitted patients remission was attained. However, in the group of patients that at baseline already met the remission criterion, 15% deteriorated. Interestingly, this paper was submitted one year before the remission criteria were published by Andreasen et al. (2005). Subsequently, Wunderink et al. (2007) reported from a retrospective study that, although a substantial percentage of the patients reached the remission criterion, remission did not lead to a higher self reported quality of life. Van Os et al. (2006) used 7 items of the BPRS to assess retrospectively the remission state in a large sample of patients with nonaffective psychotic disorders and found a shift from remission to non-remission and vice versa in about one third of the patients. Remission was,

however, not reflected in changes in quality of life parameters. De Hert et al. (2007) found an association between the remitter state and aspects of daily functioning whereas San et al. (2007) demonstrated that remission cannot be equated with adequate social- and/or vocational functioning. Finally, Leucht et al. (2007) found that both the simple criterion 'CSG severity score of mild or better' and the 50% BPRS reduction proved to be as stringent as the newly defined remission criteria.

The results from the present exploratory study show that patients who are more symptomatic and have a longer a duration of illness, do not easily reach remission and that, in a subgroup of patients, remission can be achieved by minimal partial symptomatic improvement..

Although the remission concept may be valuable, this new edition is by no means superior to the criteria as formulated by e.g. Lieberman et al. (2003), that were presented more modestly. In 2005 Remington and Kapur objected against the name 'remission criterion' since "the patient with schizophrenia who, according to these criteria, would be 'in remission' is likely to remain cognitively impaired, socially isolated, unemployed and marginalized". So far, remission is not demonstrated to be associated with improved daily functioning which justifies the explicit warning by these authors against reification of remission and also the impact it might have on the several stakeholders who are involved with patients with schizophrenia.

References

- Aleman A, Agrawal N, Morgan KD, David AS (2006). Insight in psychosis and neuropsychological function. *British Journal of Psychiatry* 189, 204-212.
- Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. *American Journal of Psychiatry* 162, 441-449.
- Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P (1995). A longitudinal study of symptom dimensions in schizophrenia. *Archives of General Psychiatry* 52:352-360.
- Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer J (1994). Five-components model of schizophrenia: Assessing the factorial invariance of the positive and negative syndrome scale. *Psychiatry Research* 52:295-303.
- Bowie CR, Harvey PD (2006). Treatment of cognitive deficits in schizophrenia. *Current Opinion in Investigational Drugs* 7, 608-613.
- Bromley E (2005). A collaborative approach to targeted treatment development for schizophrenia: A qualitative evaluation of the NIMH-MATRICES project. *Schizophrenia Bulletin* 31, 954-961.
- Bryson G, Bell M, Greig T, Kaplan E (1999). Internal consistency, temporal stability and neuropsychological correlates of three cognitive components of the positive and negative syndrome scale (PANSS). *Schizophrenia Research* 38, 27-35.
- Carlsson R, Nyman H, Ganse G, Cullberg J (2005). Neuropsychological functions predict 1- and 3-year outcome in first-episode psychosis. *Acta Psychiatrica Scandinavica* 113, 102-111.
- De Hert M, van Winkel R, Wampers M, Kane J, van Os J, Peuskens J (2007). Remission criteria for schizophrenia: evaluation in a large naturalistic cohort. *Schizophrenia Research* 92, 68-73.
- Emsley R, Chiliza B, Schoeman R (2008). Predictors of long-term outcome in schizophrenia. *Current Opinion in Psychiatry* 21, 173-177.
- Gorwood P (2005). Les critères de rémission dans la schizophrénie. *Encéphale* 31, 18-20.
- Green MF, Nuechterlein KH, Gold JM, et al. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICES conference to select cognitive domains and test criteria. *Biological Psychiatry* 56, 301-307.
- Guy W (1976). *ECDEU assessment manual for psychopharmacology*. Revised. NIMH publication DHEW Publ. NO. (Adm)76-338. National Institute of Mental Health, Bethesda, MD, pp, 217-22.
- Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G (1994). One hundred years of schizophrenia: A meta-analysis of the outcome literature. *American Journal of Psychiatry* 151, 1409-1416.
- Helldin L, Kane JM, Karilampi U, Norlander T, Archer T (2006). Remission and cognitive ability in a cohort of patients with schizophrenia. *Journal of Psychiatric Research* 40, 738-745.
- Hofer A, Niedermayer B, Kemmler G, et al. (2007). Cognitive impairment in schizophrenia: Clinical ratings are not a suitable alternative to neuropsychological testing. *Schizophrenia Research* 92, 126-131.
- Jones PB, Barnes TRE, Davies L, et al. (2006). Randomised controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. *Archives of General Psychiatry* 63, 1079-1087.
- Kane J, Honigfeld G, Singer J, Meltzer H (1988). Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry* 45, 777-796.
- Keefe RSE, Bilder RM, Davis SM, et al. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry* 64, 633-647.
- Kopelowicz A, Liberman RP, Ventura J, Zarate R, Mintz J (2005). Neurocognitive correlates of recovery from schizophrenia. *Psychological Medicine* 35, 1165-1173.
- Kay SR, Opler LA, Lindenmayer J (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Research* 23, 99-110.
- Lasser RA, Bossie CA, Gharabawi GM, Kane JM (2005). Remission in schizophrenia: Results from a 1-year study of long acting risperidone injection. *Schizophrenia Research* 77, 215-227.
- Lepine J, Piron J, Chapatot E (1989). *Factor analysis of the PANSS in schizophrenia*. Psychiatry Today: Accomplishment and promises. Excerpta Medica, Amsterdam, The Netherlands.
- Leucht S, Lasser R (2006). The concepts of remission and recovery in schizophrenia. *Pharmacopsychiatry* 39, 161-170.
- Leucht S, Beitingger R, Kissling W (2007). On the concept of remission in schizophrenia. *Psychopharmacology* 194, 435-461.
- Liberman RP, Kopelowicz A (2002). Recovery from schizophrenia: a challenge for the 21st century. *International Review of Psychiatry* 14, 245-255.
- Lieberman JA, Phillips M, Gu H, et al. (2003). Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: A 52-week randomised trial of clozapine vs chlorpromazine. *Neuropsychopharmacology* 28, 995-1003.
- Lieberman JA, Stroup S, McEvoy JP, et al. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* 353, 1209-1223.
- Lincoln TM, Lüllmann E, Rief W (2007). Correlates and long-term consequences of poor insight in patients with schizophrenia. A systematic review. *Schizophrenia Bulletin* 33, 1324-1342.

- Meltzer HY, Lee M, Cola P (1998). The evolution of treatment resistance: biologic implications. *Journal of Clinical Psychopharmacology* 18, 5-11.
- Mohamed S, Rosenbeck R, Swartz, M, et al. (2008). Relationship of cognition and psychopathology to functional impairment in schizophrenia. *American Journal of Psychiatry* AiA:1-10, Epub ahead.
- Overall JE, Gorham DR (1962). The brief psychiatric rating scale. *Psychological Reports* 10, 799-812.
- Peuskens J (1999). The evolving definition of treatment resistance. *Journal of Clinical Psychiatry* 60, 4-8.
- Remington G, Kapur S (2005). Remission: What's in a name? *American Journal of Psychiatry* 12, 2393-2394.
- Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM (2004). Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry* 161, 473-479.
- San L, Ciudad A, Alvarez E, Bobes J, Gilaberte I (2007). Symptomatic remission and social/vocational functioning in outpatients with schizophrenia: prevalence and association in a cross-sectional study. *European Psychiatry* 22, 490-498.
- Shad MU, Tamminga CA, Cullum M, Haas GL, Keshavan MS (2006). Insight and frontal cortical function in schizophrenia: A review. *Schizophrenia Research* 86, 54-70.
- Stip E (2006). Cognition, schizophrénie et effet des antipsychotiques: le point de vue d'un laboratoire de recherche clinique. *Encéphale* 32, 341-50.
- Van der Heijden FMMA, Tuinier S, Fekkes D, Sijben AES, Kahn RS, Verhoeven WMA (2004). Atypical antipsychotics and the relevance of glutamate and serotonin. *European Neuropsychopharmacology* 14, 259-265.
- Van Os J, Drukker M, A Campo J, Meijer J, Bak M, Delespaul P (2006). Validation of remission criteria for schizophrenia. *American Journal of Psychiatry* 163, 2000-2002.
- Verhoeven WMA, Van der Heijden FMMA, Wijers FWHM, Tuinier S (2005). Novel antipsychotics: Facts and fictions. *Clinical Neuropsychiatry* 2, 212-22.
- Wunderink L, Nienhuis FJ, Sytma S, Wiersma D (2007). Predictive validity of proposed remission criteria in first-episode schizophrenic patients responding to antipsychotics. *Schizophrenia Bulletin* 33, 792-796.