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What could be learned from a decade with standardized remission criteria in schizophrenia spectrum disorders: An exploratory follow-up study

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ABSTRACT

A decade has passed since the standardized remission criteria of schizophrenia spectrum disorders—the Andreasen Criteria—were defined. Over 2000 studies have been published, but only a few describe symptomatic remission over time. In this prospective study we followed patients for 3 and 5 years, respectively. The aim was to investigate how different symptoms affect the occurrence of remission and how the remission cut-off level affects remission sustainability.

The participants were patients diagnosed with schizophrenia spectrum disorders (DSM-IV). First, the importance of each core symptom for remission was examined using the Positive and Negative Syndrome Scale ($n = 274$). Second, we investigated which items affect patients to either go in and out of remission or never achieve remission ($n = 154$). Third, we investigated how the sustainability of remission is affected by a cut-off set to 2 (minimal) and 3 (mild) points, respectively ($n = 154$).

All core symptoms affected the occurence of remission, to a higher or lesser extent. Delusions and Hallucinatory behavior contributed the strongest to fluctuation between remission and non-remission, while the contribution of Mannerism and posturing was very marginal. Negative symptoms were enhanced when remission was never achieved. Moreover, the study found that remission duration was significantly longer for the cut-off score 2 rather than 3.

The study shows that, over time, remission criteria discriminate between being stable, unstable, or never in remission. Patients with only a minimal occurrence of symptom intensity exhibit a significantly longer remission duration compared to patients with mild symptom intensity, indicating that the treatment goal should be minimal symptom intensity.

1. Background

Traditionally, schizophrenia spectrum disorders have been regarded as chronically disabling, with minimal prospects for improvement. However, contemporary understanding of the heterogeneous disorders is more optimistic and encompasses treatment goals such as remission and recovery (Kane, 2001; Liberman et al., 2002). Against the background of new insights and treatment objectives, there is a growing need to better assess, communicate, and secure treatment quality. In April 2003, a working group in the US, the Remission Schizophrenia Working Group (RSWG), was therefore appointed to work on a proposal for consensus on remission and remission criteria for schizophrenia spectrum disorders (Andreasen et al., 2005). In February 2004, an international meeting took place where the RSWG's proposal was submitted to a European group of experts who reviewed and agreed on the consensus criteria. In March 2005, a proposal of a consensus definition of symptomatic remission was finally published together with operational criteria for assessing remission status in patients with schizophrenia spectrum disorders (Andreasen et al., 2005).

The RSWG defines remission as a state of symptomatic improvement characterized by current symptoms being so mild that they in themselves do not limit an individual's ability to manage activities of daily living (ADL). Three issues were central to the development of the concept: which diagnosis-specific *core symptoms* to include, what the *cut-off point* for remission should be, and for *how long* the condition should be stable before the patient is considered to be in remission. According to the Diagnostic and Statistical Manual of Mental Disorders—fourth edition (DSM-IV), the remission criteria are based on three established dimensions of psychopathology (psychoticism,

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disorganization, and negative symptoms), from which the diagnosis-specific symptoms spring (APA, 2000). The diagnosis-specific symptoms are delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (Bilder et al., 1985; Liddle, 1987; Liddle et al., 1989; Andreasen et al., 1995).

The consensus for symptomatic remission that was developed identified eight core symptoms as the basis for the remission criteria: delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/apathetic withdrawal, lack of spontaneity and flow of conversation, mannerism and posturing, and unusual thought content. For patients to be considered in remission, the cut-off for these core symptoms was set to a maximum of 3 points, corresponding to mild symptom intensity. Finally, to be considered in remission, the duration of mild or lower symptom intensity was set to at least 6 months (Andreasen et al., 2005). The criteria have been validated as user-friendly and feasible both in clinical trials and in clinical practice (van Os et al., 2006a).

The symptom-based remission criteria can be identified by any of the following three validated and established instruments: the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Scale for the Assessment of Positive Symptoms/Scale for the Assessment of Negative Symptoms (SAPS/SANS; Andreasen and Olsen, 1982; Andreasen, 1982), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962).

Since the consensus proposal, the remission criteria for schizophrenia spectrum disorders have become established and used in research as well as in clinical contexts. Furthermore, continued clarifications and validations of the concept, based on available medical studies and cross-sectional studies, have been published (Lasser et al., 2005; Helldin et al., 2006; Helldin et al., 2007). The Diagnostic and Statistical Manual of Mental Disorders—fifth edition (DSM-5) recommends that the criteria be used as part of the diagnostic procedure (APA, 2013). A search on Pubmed.gov on June 2017, yielded 2053 hits for the keywords "schizophrenia + remission".

Research undertaken in the field of schizophrenia spectrum disorders and remission has shown the benefits of remission, not only from patient and family perspectives but also from a socio-economic perspective (Hjortsberg et al., 2011). Several studies found a correlation between being in remission and higher neurocognitive capacity (Helldin et al., 2006; Torgalsbøen et al., 2014), higher functional capacity (Helldin et al., 2007; Olsson et al., 2016), better social functioning (Lasser et al., 2007), better perceived quality of life (Helldin et al., 2008; Haro et al., 2014), and less family burden (Hjärthag et al., 2008). The disorders are nevertheless characterized with a high relapse rate, and those patients at risk difficult to identify in advance (Emsley et al., 2013).

Despite a strong demand for longitudinal studies on the concept of remission (van Os et al., 2006b; Lasser et al., 2007), only a few exist. One is by Marchesi et al. (2014) who, retrospectively and based on the remission criteria, studied 48 patients at baseline and at follow-up 16 years later. Patients who achieved remission had milder symptom severity at onset. Furthermore, Marchesi et al. (2015a, 2015b) investigated the prognostic value of each core symptom at baseline, where especially low negative symptoms increased the likelihood to reach long-term remission, consistently suggested by literature (Breier et al., 1991; Ho et al., 1998; Marchesi et al., 2015a, 2015b). Moreover, the number of items that already at baseline met the remission criteria was higher for those who later achieved remission. One of the core symptoms, social withdrawal, also turned out to have a negative correlation with being in remission at follow-up. Not only remission status, but also the severity of the core symptoms at baseline, could contribute to define a subgroup of patients with a better course of illness (Marchesi et al., 2014).

The purpose of this study is to provide knowledge through a longitudinal use of the remission criteria using the PANSS instrument. First, we investigate how the different PANSS items co-vary with the presence of remission. More specifically, we examine whether the eight core symptoms contribute equally in determining remission status. Furthermore, based on the PANSS scale, we conduct an exploratory assessment of 14 of the 22 remaining symptoms, all of which are strongly associated with the occurrence of psychotic activity, in order to identify whether the use of one or more of them would significantly affect remission status. Second, we study which core symptoms that primarily cause patients to move in and out of remission, and if these symptoms differ from the core symptoms contributing to some patients never achieving remission during the measurement period. Last, we analyze the importance of the cut-off level for patients' remission status over time (3 and 5 years, respectively) if cut-off is set to 2 or 3 points for the eight core symptoms.

2. Materials and methods

2.1. Procedure

The Clinical Long-Term Investigation of Psychosis in Sweden (CLIPS) is an ongoing naturalistic follow-up study of patients diagnosed with schizophrenia spectrum disorders (schizophrenia, schizoaffective, and delusional disorders). CLIPS is a prospective study, with annual assessments of the patients with a follow-up time of 20 years. All data is collected through personal assessments exerted by standardized trained case managers. Recurrent education and co-rating training on the PANSS instrument were conducted for all case managers. Educational video recordings were used, and an allowed maximum deviation from the suggested correct answer was +/− 1.

As the patients have been recruited to the study at different times and the participation time for each patient varies, the total time for the data collection is normally longer than the data used for this particular study. Since year 2000, a total of 501 participants have been included in the CLIPS-study. The inclusion criteria were that the patients met the DSM-IV criteria for schizophrenia or other continuous psychotic disorders; did not have a comorbidity in the form of autism, mental retardation, or addiction; and, at the time of inclusion, were in a stable condition representative of the status when their illness was in its mildest form. Even though the remission criteria was developed for schizophrenia per se, and not for schizophrenia spectrum disorder, there are several studies emphasizing the long-term instability of diagnoses within the schizophrenia spectrum disorder (Helmes and Landmark, 2003). For this study, ANOVA analyses (Bonferroni corrected) with the diagnosis group (schizophrenia, schizoaffective, and delusional disorders) as the independent variable and the eight core symptoms as dependents, showed no significant differences between diagnosis groups. This is why we include the entire spectrum in the present analyses, as it reflects the clinical living as well as it includes a higher number of participants in the study.

The patients included in the current study were rated between 2004 and 2011—either at baseline or at recurring annual ratings. For patients rated at baseline, the remission concept was applied so that any remission would be documented at least 6 months before the assessment date. For patients previously rated in the study, remission duration was increased to previous year's assessment. In the study this is reported as the 1-to 5-year follow-up period. In addition to remission status, we also took into consideration other health care contacts, medical adjustments, and hospitalizations between assessments. If a patient was in remission at two subsequent assessments but other data contradicted this, we did not consider the patient to be in remission because the time criterion was not met.

2.2. Instrument

2.2.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS consists of 30 items categorized in three distinctive groups of symptoms (positive, negative, and general symptoms; Kay et al., 1987; Lindström et al., 1994). The validity and interrater reliability

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