

REVIEW

## Symptomatic Remission Along the Clinical Psychosis Spectrum: A Historical and Conceptual Review

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### ABSTRACT

**Introduction:** In this review, a historical and conceptual panorama of symptomatic remission will be provided with a focus on the whole clinical psychosis beyond schizophrenia.

**Methods:** We included all published articles on remission in psychosis, without any restrictions regarding language or year. We used a string to detect relevant articles in PubMed. We reviewed the abstracts to exclude out of scope results. Then, we evaluated the remaining articles to extract data. Variables included year of publication, language of publication, country of origin, type of article, main topic of research, main disorder studied, and reference to remission criteria.

**Results:** The final dataset included 439 citations which dates back to 1950. The Remission in Schizophrenia Working Group (RSWG) criteria which was proposed in 2005 had a major effect on remission research in schizophrenia. The RSWG criteria changed the yearly published numbers of research, the main land of remission research and the scope of the

articles. After 2005, the number of publications rapidly increased, and English became the primary language of the articles. Beyond prominent clinical effect, the criteria did have little impact on functional remission in schizophrenia. And also research in the last decade provided very few information about remission in other clinical aspects of psychosis spectrum including acute, transient and chronic forms. Furthermore, although there has been a conceptual unity in the last decade the heterogeneity of the studies is still far from decreasing, which still blurs the efforts to evaluate remission in psychosis.

**Conclusion:** Although studies on remission in schizophrenia started in the 1950s, the criteria published in 2005 changed the whole area. However, remission discussions are not yet valid for psychotic diagnoses other than schizophrenia and are limited.

**Keywords:** Psychosis, schizophrenia, remission

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### INTRODUCTION

Psychotic symptoms such as delusions, hallucinations and disorganisation manifest across the clinical psychosis spectrum. They are defining features of schizophrenia spectrum disorders, and variable features in mood and substance use disorders (1). The total lifetime prevalence of disorders with psychotic symptoms was reported to be 2.6% in Turkey (2), whereas the lifetime prevalence of schizophrenia, the prototype of psychotic disorders, is estimated to be around 0.7% (3). Psychotic symptoms lead to deterioration in social, cognitive and occupational functioning of patients, and therefore represent a significant cause of healthcare and economic burden (4). Schizophrenia has been among the top causes of disability worldwide, at least for the last three decades (5), as a result of its defined persistency of symptoms that usually start at a young age. It has traditionally been seen as a chronic debilitating disorder with a poor outcome (6), and the aim of treatment has mainly been preventing relapses. However, recent studies reveal that with current treatment opportunities, prognosis may be better than commonly assumed and that the outcome is heterogeneous (7). Nevertheless, clinical recovery is still not seen as an attainable goal for a significant proportion of schizophrenia patients (8). Current pharmacological treatments and psychosocial interventions mainly target improving the functional outcome and sustaining the state of remission.

Remission is generally defined as the state of disorder during which the patient does not manifest clinically important symptoms (9). In the context of schizophrenia treatment, the term remission had been vaguely used without defined criteria for a long time. Standardising the definition of remission in schizophrenia has been a challenging process because symptom severity and functional outcome differ significantly from patient to patient, and also because the natural course of the disorder is to alternate between acute psychotic episodes with predominantly positive symptoms and stable phases with predominantly negative symptoms. Various sets of remission criteria were defined for acute and chronic schizophrenia patients, starting from the 90's (10). Most of them were designed for identifying prognostic factors of remission instead of establishing operational criteria (11). In 2005, the Remission in Schizophrenia Working Group (RSWG) proposed the most widely accepted remission criteria, which focus on three core dimensions of the disorder (negative symptoms, disorganisation, psychoticism), and require that the patient achieves a symptom severity of 3 or less for eight core items of the Positive and Negative Symptom Scale (PANSS) for at least six months (11).

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The RSWG criteria, also known as the Andreasen criteria, mainly focus on symptomatic remission (11). However, symptomatic remission is not always equivalent to improved functioning in patients with schizophrenia. Only around one-third of patients with symptomatic remission also reach functional remission (12, 13). Various scales, not specific to schizophrenia, have been used to measure the level of functioning. In 2009, the Functional Remission of General Schizophrenia Scale (FROGS) was specifically developed for the measurement of functional remission in schizophrenia (14). Nevertheless, consensus on the definition of functional remission in schizophrenia is yet to be achieved.

The establishment of standard operational criteria for defining symptomatic remission in schizophrenia proved to be useful over the last fifteen years. The RSWG criteria have been retrospectively applied to datasets from different clinical studies. In such studies, 60–70% of the patients who were considered clinically stable did not meet the remission criteria at baseline. However, after treatment, 20–45% of these patients achieved remission and their functioning and quality of life improved (15, 16). These findings show that the RSWG criteria set an achievable treatment goal, and ameliorate the outcome even of symptomatically stable patients.

In summary, using a standard definition of remission provides a framework for designing and comparing studies, evaluating the effectiveness of interventions, and also for aiming at an outcome goal in the long-term treatment of schizophrenia (10). However, there is still no consensus on remission in other psychotic disorders ranging from schizoaffective disorder to brief psychosis, and also in the area of attenuated forms of psychosis. In this paper, we aim at providing a historical and conceptual review of remission in the clinical psychosis spectrum, with an inevitable emphasis on schizophrenia. The objective of this article is to review the use of the term ‘remission’ in the extant schizophrenia and psychosis literature from around the world, starting at the very first time the topic started being discussed.

## METHODS

In order to provide a historical and clinical review, we included all published articles on remission in psychosis, without any restrictions regarding language or year. We used the following string to detect relevant articles in PubMed: [(remission [Title]) AND ((schizophrenia [Title]) OR (psychosis [Title]) OR (psychotic [Title]) OR (schizoaffective [Title]) OR (delusional [Title]) OR (brief [Title]) OR (transient [Title])))]. We reviewed the abstracts to exclude out-of-scope results. Then, we evaluated the remaining articles to extract data. The variables used were as follows: year of publication, language of publication, country of origin, type of article (research, opinion, review, systematic review, meta-analysis, case-report, other), main topic of research (antipsychotic response, intervention response, cross-sectional rate, neuroimaging, neurocognitive state, first-episode, other), main disorder studied (schizophrenia, bipolar disorder, schizoaffective disorder, other psychotic disorder), reference to RSWG criteria. The statistical analyses were performed using SPSS version 23.0.

(delusional [Title]) OR (brief [Title]) OR (transient [Title]))]. We reviewed the abstracts to exclude out-of-scope results. Then, we evaluated the remaining articles to extract data. The variables used were as follows: year of publication, language of publication, country of origin, type of article (research, opinion, review, systematic review, meta-analysis, case-report, other), main topic of research (antipsychotic response, intervention response, cross-sectional rate, neuroimaging, neurocognitive state, first-episode, other), main disorder studied (schizophrenia, bipolar disorder, schizoaffective disorder, other psychotic disorder), reference to RSWG criteria. The statistical analyses were performed using SPSS version 23.0.

## RESULTS

The PubMed search yielded 516 citations. After excluding out-of-scope results, the final dataset included 439 citations (Figure 1).

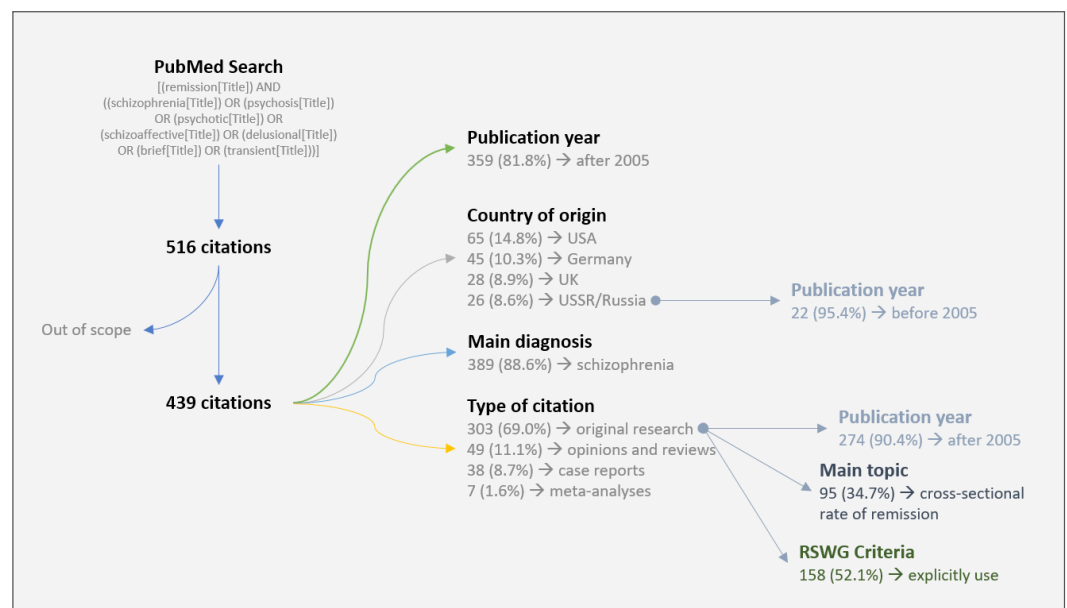
### The Historical Aspects of Articles on Remission in Psychosis

The first article on remission in psychosis was published in 1950. After only a few publications per year, the number of annually published articles increased to nine in 2005, the year the consensus criteria were published by the RSWG – and that was the highest yearly number in 55 years. The number continued to increase until it reached a peak of 35 in 2013, and started to decrease gradually after that. A further 82% (n: 359) of the articles were published after 2005. Nearly half of the early publications (n: 22/46) between 1950 and 1991 were in Russian. After the publication of the RSWG criteria, the leading country in remission in psychosis research changed to USA (n: 65, 15%), followed by Germany (n: 45, 10%), and 93% (n: 334) of the articles were published in English. The remaining articles originated from 28 different countries.

### Subtypes of Articles

The majority of the articles were on remission in schizophrenia (n: 389, 89%). There were only 14 articles on remission in affective psychosis including bipolar disorder, schizoaffective disorder and depression with psychotic features. The rest of the articles only indicated an umbrella diagnosis of “first-episode psychosis”, not a specific one. The citations included 303 original research articles (69%), 49 opinions and reviews (11%), 38 (9%) case reports, and 7 systematic reviews or meta-analyses (2%). A total of 90% (n: 274) of the research articles were published after the advent of the RSWG criteria, and the main research topic was cross-sectional rates of remission in schizophrenia (n: 95; 35%). Other research topics included rate of remission in first-episode psychosis (n: 47; 17%),

**Figure 1.** The results of PubMed search for “psychosis and remission”



remission rate as a function of antipsychotic response (n: 41; 15%), neurocognition as a function of remission (n: 25; 9%), and neuroimaging (n: 15; 6%). There were only ten studies on remission as a function of intervention (e.g. electroconvulsive therapy, cannabinal, implementation of a rehabilitation programme) response.

### The Impact of the Remission in Schizophrenia Working Group Criteria

The number of publications on remission in psychosis significantly increased after the RSWG proposed the consensus criteria in 2005. Only 29 original research articles were published between 1950 and 2005, whereas 274 were published in the last fifteen years. Only 36% (n: 29/80) of the papers published before 2005 were original research articles, whereas the ratio increased to 76% after 2005. In the last 15 years, 75% (n: 321) of the relevant articles, reviews and case reports utilised the criteria. The RSWG criteria were explicitly used in 52% of the research articles. The other research articles used other criteria or did not report any criteria regarding remission. Nevertheless, the number of manuscripts mentioning remission without documenting specific criteria has fallen in fifteen years.

### The Systematic Reviews and Meta-Analytical Work in the Field

Systematic reviews and meta-analytical articles on remission rates in psychosis emerged after the proposal of the RSWG consensus criteria. Five meta-analyses and two systematic reviews have been published since 2007 (5, 8, 17–21). Remission rates from antipsychotic drug trials of patients with schizophrenia, individuals at clinical high-risk for psychosis, and patients with first-episode psychosis were used for meta-analyses. One of the main outcomes of meta-analyses was heterogeneity in evaluation and measurement of symptomatic remission in regard of time period and method. Remission rates based on criteria were 31% in acutely ill patients with schizophrenia, 58% in patients with first-episode psychosis, and 35% of the clinically high-risk subjects (18, 20). Predictors of remission were detected with heterogeneous methods, but mainly included better premorbid function, rapid antipsychotic treatment response, lower symptom severity (not only positive but also negative and cognitive symptoms), and shorter duration of untreated psychosis (19, 21).

## DISCUSSION

In this paper, we reviewed the use of the term ‘remission’ in the psychosis literature, regardless of diagnosis, over a period spanning 70 years. As any review on this issue, we used the 2005 RSWG criteria as a turning point in remission research in psychosis. In order to provide a historical and conceptual review, we did not only review the studies that utilised the RSWG criteria, but also included all articles without any language or date restrictions. Although the publications were mainly concentrated in English-speaking and Western European countries, the interest in remission in psychosis seems to be scattered globally with articles originating from 28 countries. Nearly half of the publications between 1950 and 1991 were in Russian, which may indicate a particular and neglected interest in Soviet psychiatry concepts of remission.

The interest of Soviet psychiatry in remission is noteworthy and probably was neglected due for political reasons. Mainly focused on clinical and conceptual aspects, Soviet psychiatrists published case-reports and opinions until 1991. There was no similar interest in remission on the part of Russian psychiatry after the collapse of the Soviet Union. The growing number of publications from Germany in the last two decades also indicates a rising interest outside the English-speaking part of Europe.

The proposal of the RSWG criteria in 2005 had a significant impact on remission topics in the psychosis literature. It is worthwhile to note that

there was almost no research article before the advent of the RSWG criteria. After 2005, the number of publications rapidly increased, and English became the primary language of the articles. The consensus criteria not only flourished as part of an extensive research effort, but also meta-analytical articles and systematic reviews emerged on remission rates in psychosis after 2005. In 2012, Gorwood and colleagues compared studies about remission in schizophrenia before and after the RSWG criteria were proposed. They found a substantial decrease in the number of manuscripts using remission without a standard definition, and an increase in manuscripts using the RSWG criteria (22). The RSWG criteria almost recreated the whole research field.

The proposal and impact of the RSWG criteria can be regarded as a delayed outcome of second-generation antipsychotics. As the subtypes of citations indicate, main use of the RSWG criteria is drug trials. Particularly, the criteria provided a quasi-solid base for researchers in the field of developing novel forms of antipsychotics (e.g. long-acting depot). This trend and common use of the RSWG criteria probably has led to a concentration of studies on the clinical or symptomatic outcomes of the research on remission rather than functional and social outcome.

Functional remission is an important outcome; however, there is no consensus on its definition yet. Studies and reviews investigating the relationship between symptomatic and functional remission have yielded conflicting results. Another review published in 2010 concluded that patients in symptomatic remission had better cognitive performance, quality of life and level of functioning (23). A study of a large sample of patients with non-affective psychosis revealed that stable remission or moving into remission (based on the RSWG criteria) over time was associated with a favourable functional outcome (24). In contrast, another study comparing the functioning of schizophrenia spectrum patients who are remitted according to the RSWG criteria with patient who were not remitted showed that remission status was not associated with functional recovery (25).

The publication of the RSWG criteria can be considered a significant contribution to the schizophrenia literature and has set an attainable goal for schizophrenia treatment. Defining operational criteria that can be used to assess other patients among the clinical psychosis spectrum will provide similarly clinically meaningful outcome measures, which likely will promote more research on remission. However, another effect of the increasing dominance of the RSWG criteria seems to be associated with diagnostic narrowing. The majority of the remission research was conducted with a relatively narrow focus on schizophrenia, which excludes broader expressions of the clinical psychosis spectrum which are important from a clinical, numerical and public health perspective. Furthermore, when drug-oriented research is excluded, few efforts remain in researching remission along the clinical psychosis spectrum. Future research will be more valuable with a focus on the full clinical spectrum of psychosis.

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