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Symptomatic remission and functional recovery in patients with schizophrenia

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Update by topics

SUMMARY

A recently-proposed definition for remission and recovery in schizophrenia is receiving increased attention from clinicians and researchers. The interest in these issues is based on the recently-proposed definition of symptomatic remission, and the development of operational criteria for its assessment, by the Remission in Schizophrenia Working Group (RSWG) in the United States in 2005. Remission is assessed using eight items of the Positive and Negative Syndrome Scale (PANSS), all of which have to be scored with a symptom severity of ≤3 points (mild or better), sustained for a minimum duration of six months. In Europe, proposed definition criteria about response and remission were introduced in 2006. Response can be assessed, with the PANSS, using a cut-off of at least 50% reduction of the baseline score for the acutely ill, and a cut-off of at least 25% reduction for refractory patients. Remission could be assessed using a formula for calculating percentage PANSS reduction from baseline. Definition criteria have also been introduced to assess functional recovery that includes the combination of clinical and social outcomes for two consecutive years, including dimensions such as psychosocial functioning, cognition, and quality of life.

The purpose of this review is to examine existing research on symptomatic remission and functional recovery in schizophrenia. We included clinical and epidemiological studies, reviews and meta-analyses published between January 1970 and July 2013. Sixty two studies on remission and recovery were included, with a total of 94 940 patients, comprising six months' to 37 years' follow-up. Thirty two studies on functional recovery were included, with a total of 6 483 patients with a range of six months' to 42 years' follow-up. Research indicates that symptomatic remission can be achieved in 20%-97%, and functional recovery in 10%-68% of people with schizophrenia. The use of remission and recovery criteria has been recommended for clinical practice and scientific research.

Key words: Symptomatic remission, functional recovery, symptomatology, psychosocial functioning.

RESUMEN

Recientemente los conceptos de remisión sintomática y recuperación funcional en los pacientes que padecen esquizofrenia han recibido una considerable atención por parte de los clínicos y los investigadores. El interés en estos aspectos tiene que ver con la propuesta realizada en el 2005 por el "Grupo de trabajo para evaluar la remisión en esquizofrenia", con el objetivo de proponer una definición de remisión sintomática, así como el desarrollo de criterios operacionales para su evaluación. La remisión sintomática se evalúa utilizando ocho reactivos de la escala PANSS, los cuales deben puntuar tres o menos, con una duración mínima de seis meses de remisión. En Europa, desde el 2006, también se han propuesto criterios para evaluar la respuesta al tratamiento, así como la remisión sintomática. La remisión se puede evaluar usando una fórmula para calcular el porcentaje de reducción de síntomas desde el inicio del tratamiento de acuerdo al PANSS.

También se han desarrollado criterios para evaluar la recuperación funcional que incluyen la combinación de aspectos clínicos y psicosociales, que se deben mantener por lo menos por dos años consecutivos, incluyendo dimensiones como el funcionamiento psicosocial, el funcionamiento cognitivo y la calidad de vida. En el presente artículo se revisa la investigación respecto a los conceptos de remisión sintomática y recuperación funcional en los pacientes afectados por esta patología, incluyendo estudios clínicos, epidemiológicos, estudios de revisión y meta-análisis publicados entre enero de 1970 a julio de 2013. Se incluyeron 62 estudios sobre remisión sintomática/recuperación funcional, con un total de 94 940 pacientes, con un seguimiento de seis meses a 37 años. También se incluyeron 32 estudios de recuperación funcional, con un total de 6 483 pacientes, con un seguimiento de dos a 42 años. Los resultados indican que entre el 20 y el 97% de los pacientes pueden lograr la remisión sintomática, mientras que entre el 10 y el 68% alcanzan la recuperación funcional. Se ha recomendado el uso de estos criterios en la práctica clínica y en la investigación científica.

Palabras clave: Remisión sintomática, recuperación funcional, sintomatología, funcionamiento psicosocial.

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INTRODUCTION

Schizophrenia is a serious and complex mental illness, of a chronic, heterogeneous, and unpredictable nature. Those who have it must struggle with the psychotic symptomatology, incapacity, disability, and disadvantage it causes in cognitive deterioration, psychosocial function, and quality of life. Other problems include incorrect use of anti-psychotic medication in up to 75%[1,2] of those with the condition, which can cause relapses in up to 70%[3] and secondary effects in some 70%.[4] Clinical studies using anti-psychotic medications have to some extent allowed an assessment of their effectiveness on what has been called the "response to treatment", and also, to measure the remission of psychotic symptomatology, an aspect called "symptomatic remission", which is considered a fundamental condition for "functional recovery".[5-8] Negative symptoms – another important clinical manifestation – are a permanent problem, and up until this point a way of mitigating, eliminating, or controlling these has not been found. A recent article with the illustrative title "Negative symptoms of schizophrenia: a problem that won't disappear"[9] revises the studies and instruments for their assessment. It proposes that such symptoms are debilitating and disabling, and although they sometimes improve with anti-psychotic medication, the final result is not very encouraging, given that until now, pharmacological treatments have not controlled this symptomatology satisfactorily.

Further to the psychotic symptomatology, schizophrenia causes a "marked social and working dysfunction",[10] considered a relevant characteristic of the illness that causes unease and deterioration in psychosocial function, and it is this poor or deficient function that identifies people as schizophrenic.[11] These considerations paved the way for research into the psychosocial component,[12] assessing the function/dysfunction of the patient as an important component of their recovery. As such, scientific research has developed a wide variety of psychosocial treatments which complement antipsychotic medications;[13-18] their efficacy, both in clinical improvement and psychosocial function, sets out new perspectives on the aforementioned concepts of "symptomatic remission" and "functional recovery". An example of this is the emergence of effective comprehensive, pharmacological, and psychosocial treatments, reinforced by so-called "evidence-based medicine". Various revisions on this aspect[19-27] conclude that a person with schizophrenia should benefit from a combination of various alternatives to treatment: a) an optimal dose of antipsychotic drugs, b) psychosocial interventions such as learning psychosocial skills, help to work, various approaches to managing the illness, adhering to medication, etc., c) psycho-education for both the patient and their family on how to manage the illness, prevention of relapses, learning coping strategies for crisis situations, conflict resolution in the home and the community, and d) cognitive interventions such as cognitive behavioral therapy, cognitive rehabilitation, and *cognitive remediation*. Liberman, that pioneer of psychosocial treatments and functional recovery, assumed that the evidence available with respect to treatments that seek optimal management of symptoms and psychosocial reintegration of the patient, did not allow any conclusion as to the level that would be reached by these advances in treatment and rehabilitation in terms of the schizophrenia patient's functional recovery as a realistic and currently-achievable goal.[28] Research in this area is therefore very important, and as such he proposes certain criteria for assessing functional recovery.[28]

To approach this theme, some contextualization of the situation is necessary for these patients who, until 70 years ago, were locked up for life in asylums and mental institutions, with no possibility of return to their communities. "Symptomatic remission", therefore, was practically non-existent due to the lack of medications to treat this condition; nor was there any concept of "functional recovery". Later on, thanks to the appearance of neuroleptic medications in the 1950s, a reduction, and in some cases considerable remission was achieved in symptomatology, thus initiating the concept of "symptomatic remission". As a consequence of this, patients could be discharged from the psychiatric hospitals and live in the community; a process that was called "deinstitutionalization". Furthermore, and due to the effective control of symptomatology, upon finding themselves within the community, patients had to go through a new process of "social reinsertion", which also implied resolving issues such as finding a place to live, working to support themselves, socializing in order to have a support network, establishing effective friendships and relationships, and managing family relationships. From a medical and specifically psychiatric perspective, the approach was to keep the patient clinically stable, and from a psychosocial perspective, to enable them to function within the community. As such, and from the clinical perspective, the aim was the reduction and remission of symptoms in order to achieve a "sustained remission" in such a way that patients could keep themselves stable. From the psychosocial perspective, the object was to enable patients to learn psychosocial skills to improve their functioning within the community, thus integrating the biological, psychological, and social components in what is currently known as the biopsychosocial focus on schizophrenia.

There are considerations that schizophrenia is a chronic illness with unfavorable results,[29] or that it is an illness of the brain for which there is not much hope for recovery. It is associated with clinical, cognitive, social, and vocational deterioration and furthermore, patients do not have friendships, partners, or work for years at a time. These considerations raise questions around whether recovery from schizophrenia is a myth,[30] or whether it is realistic for patients to believe that they could recover from their illness.[31] According to Kraepelin, the possibility of achieving recovery was thought of as rare or impossible, given that it was considered an irreversible, un-

treatable, and incurable condition. However, advances over the last 50 years have allowed this pessimistic perspective to change into a moderately optimistic one, in that symptomatic remission can be considered a realistically achievable goal,[32-34] as is the case with functional recovery.[35-39]

These considerations raise questions such as: how do you define symptomatic remission? How do you define functional recovery? How do you measure these aspects? How many patients manage to achieve symptomatic remission and/or functional recovery?

OBJECTIVE

The aim of this present work is to revise the research with respect to the concepts of symptomatic remission and functional recovery in schizophrenia, the proposals of criteria for their use in clinical practice and scientific research, and to present results on the percentage of patients who present symptomatic remission and functional recovery in accordance with the studies revised.

METHOD

A systematic revision was carried out of the scientific literature published between January 1970 and July 2013, using the following search terms: schizophrenia, first psychotic episode, remission, symptomatic remission, remission in schizophrenia, psychosocial remission, symptomatic recovery, anti-psychotic medications, response to pharmacological treatment, recovery, and functional recovery. The revision gave a result of a total of 160 studies, of which 17 were eliminated as they did not meet the criteria established in terms of the search terms or the objectives of the study. This left a total of 143 articles which were divided into 61 studies on symptomatic remission of a total of 94821 patients comprising between six months' and 37 years' follow-up, and 32 studies on functional recovery of a total of 6483 patients comprising between six months' and 42 years' follow-up.

The results are presented using clinical and epidemiological studies, revision and meta-analysis articles included in the following databases: Medline, Psychiatry, EBM Reviews, PsychINFO-APA, Psychology & Behavioral Sciences, Base Salud en Español, CC Clinical Medicine, CC Social and Behavioral Sciences, Medic Latina, Elsevier Science Direct, The Cochrane Library, Biblioteca Cochrane Plus, Ciencias de la Salud-BIREME, World Health Organization, and Science Electronic Library Online.

Considerations and definitions around "symptomatic remission"

The landscape of this area of study is relatively indefinite, due to the fact that there is still not a set of universal criteria to assess symptomatic remission. In an attempt to resolve this situation, since 2005, two study groups, one in the United States and one in Europe, have proposed the introduction of what have been called "new criteria" to define symptomatic remission in schizophrenia.

In the US, Andreasen and a group of experts on the subject comprised the "The Remission in Schizophrenia Working Group".[32] The proposal of this group has been to define "symptomatic remission" as: "the state in which the patient demonstrates improvement in the signs and symptoms to such a level that at low intensity, they do not significantly interfere in their behavior, and as such, they are below the threshold used to justify the initial diagnosis of schizophrenia." The group considered various dimensions of psychopathology which can generally be identified using statistical techniques or by means of studies based on factorial analyses. Through these, they identified three psychopathological dimensions of schizophrenia: 1) psychoticism (distortion of reality), 2) conceptual disorganization, and 3) negative symptoms. They also included five criteria from the DSM-IV for the diagnosis of schizophrenia: delirious ideas, hallucinations, disorganized language, catatonic or seriously disorganized behavior, and negative symptoms, which coincided with the three dimensions of psychopathology. To assess remission, the group proposed various research instruments such as: 1) the Positive and Negative Syndrome Scale (PANSS) for schizophrenia:[40] eight symptoms, 2.) the Brief Psychiatric Rating Scale – BPRS:[41] seven symptoms, 3) the Scale to Assess Positive Symptoms – SAPS:[42] eight symptoms, and 4) the Scale to Assess Negative Symptoms – SANS:[42] eight reactives. To assess symptomatic remission, they selected eight reactives from the PANSS included in the three dimensions, considering it necessity to meet two criteria: a) the assessment of symptoms must have a score of three or less in the eight reactives selected, and b) the remission time must be a period of at least six months (table 1). The novelty of this proposal[34] consisted of using the dimensional focus to assess remission in accordance with criteria of severity; this was different from the criteria of considering improvements compared with pre- and post-treatment evaluations.[43] Furthermore, its importance comes from the fact that it does not require the total absence of symptoms, as well as considering that at least six months of remission are necessary to ensure that it is not transitory.

In Europe, the criteria to assess "symptomatic remission" have also been put forward for consideration by clinicians and researchers, including definitions of response to treatment for which cut-off points are used, and to assess remission they propose a formula that allows the percentage of symptom reduction to be calculated.[8,44-46]

"Response to treatment" has been defined as "a significant improvement in the patient's psychopathology, in spite of still being symptomatic at the end of the treatment".[43] To measure response to treatment, a wide variety of cut-off

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Table 1. Criteria proposed by a consensus of experts known as "The Remission in Schizophrenia Working Group", Andreasen et al., 2005, to assess symptomatic remission by means of eight symptoms selected from the Positive and Negative Symptoms Scale (PANSS) for schizophrenia (Kay et al., 1987)

Reactive	Type of symptom	Psychopathological component	Symptom
P1	Positive symptom	Psychoticism	Deliria
G9	General psychopathology	Psychoticism	Unusual thought content
P3	Positive symptom	Psychoticism	Hallucinatory behavior
P2	General psychopathology	Disorganization	Conceptual disorganization
G5	General psychopathology	Disorganization	Mannerism and postural attitude
N1	Negative symptom	Negative symptomatology	Numbed or dulled emotion
N4	Negative symptom	Negative symptomatology	Apathetic/passive social withdrawal
N6	Negative symptom	Negative symptomatology	Difficulty with fluid conversation

Scoring system: 1=absent; 2=minimal; 3=mild; 4=moderate; 5=moderately severe; 6=severe; 7=extreme.
Meeting the criteria for symptomatic remission must cover two aspects:
1. Severity: determined by a score of 3 or less (3=mild, 2=minimal, 1=absent) in each of the symptoms selected.
2. Time: remission must be maintained for a period of at least 6 months.

points can be considered: 20%, 30%, 40%, or 50%, using the averages at the start and end of the treatment to calculate the percentage of reduction of the symptoms. It is recommended that cut-off points be determined before interventions are carried out. Meeting the response criteria allows a knowledge of how many patients have obtained a significant clinical change. The Brief Psychiatric Rating Scale – BPRS[41] and the Positive and Negative Symptom Scale – PANSS[40] for schizophrenia have been used to verify whether the criteria are met for definition of response to treatment. It has been suggested that the percentages of response could be presented in tables that include intervals of 25%, always calculating the "reduction" of symptoms pre- and post-treatment with ranges of: less than 25%, 25%-49%, 50%-74%, and 75%-100%. These tables have frequently been used in clinical works with anti-psychotics carried out in China[47] and represent an advantage, given that they allow a good impression of the distribution of results. In order to have a more precise idea around the presentation of these tables, see Leucht.[43]

"Remission" has been defined as "the state in which the patient finds themselves free from, or without the presence of, clinically significant symptoms",[43] which reflects how many patients can present with symptomatology. A formula has been proposed in order to calculate the percentage of reduction in symptoms using the PANSS scale,[43] expressed as follows:

$$\frac{\text{(initial PANSS score–final PANSS score)} \times 100}{\text{(final PANSS score-30)}}$$

In order to use this formula, it is necessary to have patients' pre- and post-treatment assessments, comparing the experimental with the control groups. Due to it being considered that the reduction in symptoms was not calculated correctly, as recently as 2009, corrections were made to the formula, subtracting 30 points, which indicates the absence of symptoms, from the final treatment score. The use of this formula has been recommended for clinicians and researchers who are treating patients with schizophrenia.[43,45]

Due to the high number of studies found, table 2 presents a summary of the primary investigations on symptomatic remission. In accordance with various recent revisions, the percentages of remission are located between: 20%-60%,[39] 30%-70%,[48] and 17%-88%.[49] Considering the results of all the research we revised, it is concluded that the percentage for symptomatic remission is located within the range of 20%-97%.

Considerations and definitions around functional recovery

Over the past 50 years, the therapeutic aims for the treatment of schizophrenia have gradually changed, from what used to be considered important achievements in respect of modest improvement in patients such as self-care, control of aggression, and avoiding self-harm, to a more effective control of psychotic symptomatology.[34] The currently-proposed model has been called "functional recovery", a *sine qua non* condition of which is symptomatic remission. Because of this, some treatment goals in terms of achieving a rapid reduction in symptoms (remission) in the short term with the use of anti-psychotics, and achieving the clinical stability of the patient, have been overtaken and re-formulated due to no longer being considered end-of-treatment goals. As a consequence, a new feasible goal has been proposed, which is that of reaching "functional recovery"; primarily taking into account that the evidence-based treatment indicates that a considerable number of people with schizophrenia can recover, although evidently not totally. An important contribution in the study and understanding of "functional recovery" is that of Weiden and Zygmunt,[50] who developed a scheme made up of three concepts, each one with corresponding objectives. Each concept corresponds with an instance that forms part of a pyramid, at the base of which is the concept of "response to treatment", and its goal is to maintain the clinical stability of the patient. Above the base, and on a second instance is the concept of "remission",

Table 2. Investigations into symptomatic remission and functional recovery in schizophrenia

Author, year and country	Number of patients	Type of study	Results
Bleuler 1968 Zurich, Switzerland.[90]	208	Chronic patients	57% had symptomatic recovery
Tsuang et al., 1979 Iowa, USA.[91]	85	Chronic patients	46% had symptomatic recovery
Huber et al., 1980 Bonn, Germany.[92]	502	Follow-up of 6 years Duration of illness 22.4 years	22% had symptomatic remission 56% had functional recovery (full time work)
Ciompi et al., 1980 Berna, Switzerland.[93]	289	Follow-up of 37 years	49% had favorable results in the long term 27% had favorable results in behavior, occupational and social function 22% were mildly dysfunctional 15% had full time work and 37% had part time work
Ogawa et al., 1987 Gunma, Japan.[94]	140	21 and 27 years of follow-up	31% presented recovery (with no positive symptoms of schizophrenia) 46% had improved (reduced positive and negative symptoms) 74% totally productive or high-level productive
Harding et al., 1987 Vermont, USA.[57]	268	32 years of follow-up	68% improved or had recovery without the presence of positive and negative symptoms 45% did not present psychiatric symptoms
Loebel et al., 1992 Nueva York, USA.[95]	70	3 years of follow-up	Total remission (without residual symptoms): 74% Partial remission (with substantial improvements in positive and negative symptoms: 12% No remission (positive symptoms continued after the first episode): 14%
Hegarty et al., 1994 Boston, USA.[96]	51 800	Meta-analysis of 320 studies between 1895-1992	40.2% had functional recovery for 5.6 years of follow-up From 1895-1955, recovery was at 35.4%, which increased to 48.5% from 1956-1985
Lieberman et al., 1993 Nueva York, USA.[97]	118	Patients with first psychotic episode	80% had symptomatic recovery during the first year of continuous treatment
DeSisto et al., 1995 Vermont, USA.[98]	99	Patients with schizophrenia receiving medications and rehabilitation	Patients with medication improved by 49% Patients receiving medication and rehabilitation improved by 68%
McGorry et al., 1996 Victoria, Australia.[99]	200	Patients with first psychotic episode	High levels of recovery were found in symptomatology, negative symptoms, global functioning, and quality of life in patients who received a treatment with a duration less than 28 days
Edwards et al., 1996 Melbourne, Australia.[100]	98	Remission in patients with first episode	8.9% of patients remained with positive symptoms at 3, 6, and 12 months 91% had symptomatic recovery
Tohen et al., 2000 Boston, USA.[33]	219	Patients with first psychotic episode with symptoms of affective disorder	Symptomatic recovery after the first hospitalization was obtained at 3 months (65.1%), 6 months (83.7%), 12 months (91.1%), and 24 months (97.5%) Functional recovery was only obtained by a third of the patients (38%)
Harrison et al., 2001, 14 places worldwide.[35]	1633	15 and 25 years of follow-up	56% of the cohort with incidents were considered recovered 60% of the cohort with prevalence were considered recovered Around 50% did not have psychotic episodes in the last 2 years
Hoffman et al., 2002 Berna, Switzerland.[101]	75	20 patients with recovery compared with 55 cohorts	Patients with functional recovery had a lower number of negative symptoms, lower levels of disability, and lower scores in the locus of control
Whitehorn et al., 2002 Nova Scotia, Canada.[56]	103	One year of treatment, 6 and 12 months of follow-up	After a year of treatment, 67% had symptomatic recovery At 12 months' follow-up, 50% had a global functional recovery
Robinson et al., 2004 Nueva York, USA.[102]	118	5 years of follow-up in patients with first primer episodio psicótico	Symptomatic remission at 5 years: 47.2% Adequate social function for more than 2 years: 25.5% Total functional recovery for more than 2 years: 13.7%

Cuadro 2. Continued

Author, year and country	Number of patients	Type of study	Results
Kopelowicz et al., 2005 Los Angeles, USA.[62]	56	Neurocognitive recovery was compared in 3 groups: 1) 28 patients with functional recovery, 2) 28 patients without recovery 3) 26 healthy control subjects	Recovered patients had significantly better performance in executive function tests, verbal fluency, and verbal memory than those without recovery. Their performance was at a level equivalent to the healthy subjects Differences between the two groups of patients were not found in the early visual processing test. However, both groups performed worse than the healthy subjects Variables related to the functioning of the frontal lobe seem to be related to functional recovery
Liberman et al., 2005 Los Angeles, USA.[28]	2874 (21 studies)	Investigation into functional recovery	Symptomatic remission with a range of 46% to 91%
Leucht et al., 2006 Munich, Germany.[43]	2950 (6 studies)	Clinical studies on functional recovery	Symptomatic remission: 22% to 49% Functional recovery: 27% to 60%
Haro et al., 2006 Barcelona, Spain.[103]	6516	Assessing remission and relapses	Symptomatic relapse: 64.6% Being female, having a high level of social function and a shorter duration of illness were factors significantly associated with remission
Helldin et al., 2007 Trollhattan, Switzerland.[104]	243	Assessing remission and function	Symptomatic remission: 38% Patients in remission demonstrated better function in activities in daily life, better social functioning in the community, and a better use of the health services
San et al., 2007 Barcelona, Spain.[60]	1010 (100 mental health centers)	Assessing symptomatic remission and associated clinical aspects	Symptomatic remission: 44.8% Only 10.2% had adequate social and/or vocational function. Adherence to treatment, previous or current participation in psychotherapy, and the age of the patient were associated with a lower probability of achieving symptomatic remission
Holthausen et al., 2007 Groningen, Utrecht, Netherlands.[105]	103	Predictive values for success in cognition related to remission in recently-started patients	Partial remission: 43% Total remission: 25% Improvement in social function: 69% Deterioration: 9% Stability: 2%
Lambert et al., 2008 Hamburg, Germany.[106]	392	Assessing remission and recovery	Remission/Recovery Symptoms: 60.3%/51.7% Function: 45%/35% Subjective wellbeing: 57%/44%
Emsley et al., 2008 Tycerberg, South Africa.[107]	50	Assessing remission and associated aspects	Symptomatic remission: 64% Of those who had remission, 97% remained in remission which was found to be associated with improvements in symptoms, *insight*, and better social and occupational function
Addington et al., 2008 Calgary, Canada.[108]	240	RSymptomatic remission: criteria of severity and time in patients with first episode	Symptomatic remission: 36.7% Meeting with severity criteria in last assessment: 19.6% Not meeting criteria for remission: 23.3%
Eberhard et al., 2009 Lund, Switzerland.[109]	162	Assessing symptomatic remission	Symptomatic remission: 40% at the start of the study, which was maintained between 55% and 60% during the 5 years of the study, associated with the global index of the illness, insight, the social component, except in those that studied and worked
Boter et al., 2009, Utrech, Netherlands.[110]	498	Effect of anti-psychotics on achieving remission	Symptomatic remission: 17% - 41%
Wunderink et al., 2009 Groningen, Netherlands.[111]	125	Clinical recovery in patients with first episode	Symptomatic remission: 52% Functional remission: 26.4% Both criteria: 19.2%
Zimmermann et al., 2009 Greifswald, Germany.[112]	88	Frequency of remission and hospitalizations	Symptomatic remission: 12.2% Re-hospitalizations: 42.1%

Cuadro 2. Continued

Author, year and country	Number of patients	Type of study	Results
Potking et al., 2009 California, USA.[113]	599	Double-blind study to compare remission using an atypical and a conventional anti-psychotic for 196 weeks	Symptomatic remission with atypical medication: 51% Symptomatic remission with conventional medication: 40%
Rossi et al., 2009 L´Aquila, Italy.[114]	347	Assessment of remission over a year	Maintained symptomatic remission for 52 weeks of treatment: 32%
Bobes et al., 2009 Oviedo, Spain.[59]	452	Assessment of remission, function, and recovery during a year of follow-up	At the start of treatment: 22.8% met the criteria for recovery that included symptomatic remission and adequate function After one year of treatment: 88.9% maintained symptomatic remission. Of these, the proportion of patients in recovery increased to 27.1%
Wobrock et al., 2009 Gottingen, Germany.[115]	404	Assessing symptomatic remission during 12 weeks of treatment	Symptomatic remission: 58.3% Predictors for not achieving remission were: older age, multiple previous episodes, longer duration of current episode, and alcohol abuse
Henry et al., 2010 Melbourne, Victoria, Australia.[116]	723	Assess remission in patients with first episode with a follow-up of 7 years	Symptomatic remission in follow-up occurred in between 37% - 59% of patients Vocational/social recovery was observed in 31% of patients Around 25% of patients obtained symptomatic remission and social and vocational recovery
Peuskens et al., 2010 Korterberg, Belgium.[117]	195	Symptomatic remission with medications and placebo	At six months of treatment: Symptomatic remission: 76% with antipsychotic Symptomatic remission: 52% with placebo
Lambert et al., 2010 Hamburg, Germany.[118]	529 (7 European countries)	Establishing symptomatic remission and good clinical function in patients with schizophrenia	Symptomatic remission: 33% Some 21% obtained a greater symptomatic remission. The predictors were: severity of symptoms at the start of treatment, function at the start of treatment in all countries, type of schizophrenia, and a positive outlook at the start of the treatment
Jager et al., 2010 Munich, Germany.[119]	280	Response to treatment with anti-psychotics in hospitalized patients	Symptomatic remission: 45% The average duration of treatment was 54.8 days
Yeomans et al., 2010 University of Leeds, United Kingdom.[39]	1381 (8 studies)	Revision study on symptomatic remission	Symptomatic remission: 20% to 60% Patients who achieved remission have a better subjective and functional assessment
Cassidy C et al., 2010. Montreal, Quebec, Canada.[120]	141	Symptomatic remission in patients with first psychotic episode	Remission of positive symptomatology: 94%, and 84% at 3 and 6 months Remission of positive and negative symptomatology: 70%, and 56% at 3 and 6 months
Saravanan et al., 2010 Vellore, India.[121]	131	Resultados en pacientes del primer episodio psicótico	Symptomatic remission: 50% Symptomatic remission with deficits: 50%
Li et al., 2010 Taipei, Taiwan.[122]	90	Symptomatic resolution	Symptomatic resolution: 33.7% Patients with resolution had a high level of education, low scores in positive and negative symptoms, and a high level of psychosocial function
Wolter et al., 2010 Berlin, Germany.[123]	106	Remission, prediction, and stability of symptoms in schizophrenia. A 12 month study	Remission at 12 months: 13.2% Significant deterioration: 14.2% Significant improvement in psychotic symptoms: 29.2%
Ciudad et al., 2011 Madrid, Spain.[124]	6516/ 6642	Assessing remission and functional recovery	Remission: N=6516 38.2% during the first year, 64.6% during three years of follow-up Recovery: N=6641 32.5% symptomatic remission, 12.8% adequate function, 26.8% adequate quality of life
Schennach-Wolff et al., 2010 Munich, Germany.[125]	232	Symptomatic remission and subjective wellbeing under treatment with neuroleptics	Some 66% met remission criteria related with subjective wellbeing associated with the score at the start of treatment, the score on the global subscale of PANSS, secondary effects, and educational, considered as significant predictors for remission

Cuadro 2. Continued

Author, year and country	Number of patients	Type of study	Results
Brissos et al., 2011 Lisboa, Portugal Valencia y Madrid, Spain.[126]	76	Symptomatic remission, social function, quality of life, neurocognitive function	Some 30.3% presented symptomatic remission, as well as better social function, better quality of life, and a reduced level of depressive symptomatology, but did not improve in cognitive function
Ventura et al., 2011 Los Angeles, USA.[127]	77	Remission and recovery during the first year of illness	The first 6 months At the start. Symptomatic remission: 36%, Recovery: 10% At one year. Symptomatic remission: 22%, Recovery: 1%
Barak et al., 2011 Tel Aviv, Israel.[128]	295	Assessing symptomatic remission in older patients with schizophrenia	Symptomatic remission: 60% Differences were not found in the severity of psychopathology, for function upon comparing these patients with younger patients with the same diagnosis
Faber et al., 2011 Groningen, Netherlands.[129]	45	Cognitive function, remission, and recovery in the first psychotic episode	9 to 45 patients (20%) obtained a clinical recovery Of 10 patients with functional remission, 90% reached a clinical recovery Of 24 patients with symptomatic remission, 38% showed a clinical recovery
Levine et al., 2011 Ramat Gan, Israel.[130]	1332	Obtaining and maintaining remission	Remission at the start of the treatment: 16.6% Maintained remission at 6 months: 11.7% Maintained remission at 3 months: 21% Experienced remission for any length of time: 44%
Girgis et al., 2011 Nueva York, USA.[131]	160	Assessing remission	Symptomatic remission: 78%
Emsley et al., 2011 Cape Town, South Africa.[49]	Revision of 13 studies on remission and 5 on recovery	Assessment of data on remission and recovery	Symptomatic remission: 17-88% Recovery: 4-63%
Karow et al., 2012 Hamburg, Germany.[132]	131	Remission and functional improvements	Symptomatic remission: 44% Difficulties in: Social relationships: 40%. Work: 29%. Activities in daily life: 17%
Verma et al., 2012 Singapore, Singapore.[133]	1175	Symptomatic and functional remission in patients with first episode of psychosis	54.1% symptomatic remission, 58.4% functional remission, 29.4% both criteria
Mosolov et al., 2012 Moscow, Russia.[134]	203	Remission in schizophrenia: result of a study of 6 months and 1 year of therapeutic observation	31.5% symptomatic remission 26.1% complete remission
Barak et al., 2012 Tel-Aviv, Israel.[135]	445	Symptomatic and psychosocial remission	37% symptomatic remission 31% psychosocial remission
Valencia et al., 2012 Mexico City, Mexico.[69]	73	Results of a 6 months study on symptomatic remission, functional remission, and functional recovery in patients with first episode	Groups: Experimental *vs* control Symptomatic remission: 94.0%/58.8% Functional remission: 56.4%/3.6% Recovery: 56.4%/2.9%
Dahlan et al., 2013 Kuala Lumpur, Malaysia.[136]	155	Remission of symptoms in patients with schizophrenia who received assertive community treatment with a year of follow-up	Symptomatic remission: 76% Symptomatic remission was significantly associated with patients under 35 years, with a high level of education and good social support
Prikryl et al., 2013 Brno, Czech Republic.[137]	481	Prevalence of remission and recovery in schizophrenia	Symptomatic remission: 44%. Functional remission: 26%. Recovery: 19%
Valencia et al., 2013 Mexico City, Mexico.[70]	119	Symptomatic remission and functional improvements	Total sample: Symptomatic remission: 80% Functional improvements: 33%
Cannavó et al., 2013 Catania, Italy.[138]	70	*Insight* and recovery in patients with schizophrenia	Results after two years: Symptomatic remission: 50% Adequate social function: 25.5%. Total recovery: 12%

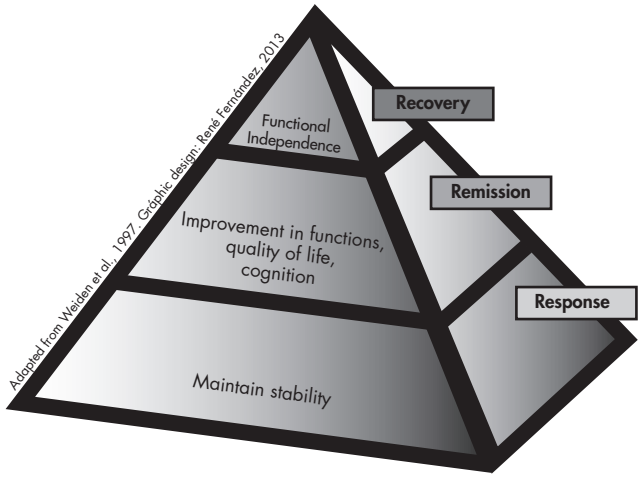

Figure 1. Functional recovery in schizophrenia.

which consists of obtaining improvement in social and cognitive function and quality of life. In the upper part of the pyramid and the final and primary instance is the concept of "functional recovery" which refers to a functional and socially autonomous patient (figure 1). Although there are various definitions of the subject of study, there is still not an international consensus in terms of having a unique definition of "functional recovery" and what that means. To illustrate this point, only some examples have been included. Recovery is considered as "the ability to function socially and vocationally in the community, as well as be relatively free from the psychopathology of the illness".[44] It can also consist of "increasing the patient's abilities to satisfactorily deal with challenges in life and manage their symptoms". The concept emphasizes the capacity of the person in order to have hope and lead a significant life that includes achieving the following aspects to the maximum extent possible: 1) achieve autonomy in accordance with desires and capacities, 2) demonstrate self-respect and dignity, 3) accept that life must include total integration into the community, and 4) resume normal development.[51] In other words, it is "the inclusion of normal levels of social and occupational function, an independent life, and remission from psychiatric symptoms".[28] Finally, it includes the testimony of a patient with schizophrenia in terms of what "functional recovery" means for them: "I would like to stay productive, be in contact with people, write letters like I used to before, have a job, clean my room, wash my clothes."[52]

Although various components have been identified, it is still not clear how the different elements of "functional recovery" can relate with others.[53] In this regard, it has been found that there are a number of models or foci: one, based on evidence, implies the approach and reduction of "objective" problems related to the illness (improvements in symptoms and function) and another based on the experience of users, that must reflect the "subjective" changes in the patient's life (improved self-esteem, rejecting the stigma of the illness).[37] The primary characteristics of these two models are illustrated in table 3.

Unlike Weiden,[50] who set out three components, specified in figure 1, other authors generally consider two important components of "functional recovery". The first is symptomatological component, which has to do with aspects such as the reduction of symptoms over the long term, symptomatic remission, sustained remission or the absence of the primary symptoms of the illness. The use of instruments previously described in the remission section is recommended in order to assess this component. The basis of the instruments is the criteria of the DSM-IV for schizophrenia, and includes various dimensions of psychopathology. The second is the psychosocial component, which implies the assessment of specific functioning such as: adequate psychosocial function, and improvements in function or a return to normal levels of function.[6,54,55] The criteria called "normal levels of function" or "good function", and which varies according to various authors, implies a score of > than 50;[56] > than 61;[57] or >65;[58] >80[59,60] on the Global Assessment of Functioning Scale.[61] Other authors consider the remission of symptoms, cognition, function, and quality of life as components on the spectrum of functional recovery.[28,36,46,50,62]

In terms of consideration for assessing functional recovery, the following criteria have been proposed: 1) a reliable diagnosis of schizophrenia during the early phases of the illness, 2) not meeting the diagnostic criteria for schizophrenia at the time of assessment, 3) not having been hospital-

Table 3. Models of functional recovery

Based on evidence	Based on user experience
Stemmed from clinic/scientific investigation	Stemmed from users: patients, families, self-help groups, ex-patients
Based on clinical interventions, integration of pharmacological treatment and psychosocial rehabilitation, family, psychoeducation, longitudinal studies	Based on reports of experiences from patients in recovery, their families and self-help groups
Aim: remission of symptoms and return to a normal level of functioning	Aim: personal development and growth. Overcome the effects of being a patient with a mental disorder. Establish a full and satisfactory life. May include remission of symptoms and functioning, but this is not a requirement
Recovery is a long-term challenge which goes beyond symptomatic remission	Recovery is a goal that consists of establishing a full and satisfactory life
Objective focus	Subjective focus
Quantitative focus and analysis	Qualitative focus and analysis
Psychiatric, biopsycho-social focus	Psychological, psychosocial focus

(Valencia, M, 2013).

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ized for at least five years, 4) psychosocial function "within normal range" with a score of >65 in accordance with the EEAG-GAF, and 5) anti-psychotic medications are not being taken, or if they are, they are at very low doses (less than half of what would be considered a daily dose).[58] The following criteria can also be considered: 1) moderate presence of psychotic symptoms in accordance with the scales that assess positive and negative symptoms, 2) an independent life, 3) working or studying at least part-time, and 4) participating in social and recreational activities. These criteria should be met for a minimum of two years,[28] which coincides with the American Psychiatric Association's Practice guideline for the treatment of patients with schizophrenia.[51] The most widely used of all these criteria in research are those proposed by the authors who report percentages of between 20%-65% of functional recovery.[28] Table 4 presents a summary of various studies of patients with schizophrenia whose results indicate the percentage of "functional recovery" between a range of 33% to 68%. However, some authors consider this between 10% and 15%.[63-66] Only three studies have been carried out in Mexico on "symptomatic remission" and/or "functional recovery" in patients with schizophrenia. In one study[67] on "functional recovery" in patients with a first psychotic episode, aimed to assess functional deterioration, psychosocial function and its relation with clinical variables, some 76 patients participated, and the Positive and Negative Symptoms Scale – PANSS[40] for schizophrenia and the Psychosocial Functioning Scale[68] were applied at the start, at six months, and at twelve months into follow-up. Improvements in psychosocial function, and a 50% reduction in the severity of psychotic symptoms was found, which indicates that the vast majority of these patients remained with functional disability for at least a year after the presentation of the first psychotic episode. It can therefore be concluded that "symptomatic" and "functional recovery" could only be reached by these patients for a limited period of time.

In the second study,[69] also carried out by patients with a first psychotic episode, symptomatic remission was assessed in accordance with the Working group criteria for remission in schizophrenia[32] and functional recovery in accordance with the criteria of Torgalsboen,[5] with a score of <65 in accordance with the Global Assessment of Functioning Scale – GAF.[61]

Table 4. Studies on functional recovery in patients with schizophrenia

Study	Place	Sample	Duration of follow-up (years)	Percentage of functional recovery
Bleuler, 1968.[90]	Germany	208	23	53-68
Tsuang et al., 1979.[91]	USA	186	35	46
Huber et al., 1980.[92]	Germany	502	22	57
Ciompi, 1980.[93]	Switzerland	289	37	33
Harding et al., 1987.[57]	USA	269	32	62-68
Ogawa et al., 1987.[94]	Japan	140	23	57
Marneros et al., 1989.[139]	Germany	249	25	58
Mala, 1993.[65]	Czechoslovakia	120	42	10
DeSisto et al., 1995.[98]	USA	269	35	49
Stephens et al., 1997.[63]	USA	484	27	13
Tohen et al., 2000.[33]	USA	219	2	38
Harrison et al., 2001.[35]	18 countries	776	25	56
Kobayashi, 2002.[140]	Japan	62	13	28
Modestin et al., 2003.[66]	Switzerland	208	23	12-15
Warner 2004.[141]	USA	110 *	20	20
Harrow et al., 2005.[54]	USA	274	15	40
Menezes et al., 2006.[142]	Canada	37	2	42
Lambert et al., 2008.[106]	Germany	392	3	44
Miettunen et al., 2008.[143]	Finland	16 **	2	32
Crumlish et al., 2009.[144]	Ireland	118	8	39
Strauss et al., 2010.[145]	USA	56	20	13
Jobe et al., 2010.[146]	USA	7 *	26	45
Ciudad et al., 2011.[124]	Spain	2 *	2-3	10-12
Bertelsen et al., 2011.[147]	Denmark	265	2	17
Abdel-Baki et al., 2011.[148]	Canada	142	10-16	15
Albert et al., 2011.[149]	Denmark	255	5	15
Valencia et al., 2012.[69]	Mexico	73	6 months	2-56
Jaaskelainen et al., 2012.[150]	Finland	50 **	2	8-20
Harrow et al., 2012.[151]	USA	139	20	17-50
Cannavó et al., 2013.[138]	Italy	70	2	12
Prikryl et al., 2013.[137]	Czech Republic	481		19

* Studies; ** Studies meta-analysis.

Functional recovery was the combination of symptomatic remission and functional remission. Some 73 patients participated in the study. Two groups were compared: patients who received antipsychotic medication and psychosocial treatment (experimental group, N-39) with a group who only received anti-psychotic medication (control group, N=34). At the end of one year of treatment, 94% of the experimental patients and 58% of the control patients obtained symptomatic remission. Functional remission was at 56% for the experimental group and 3.6% for the control group, while functional recovery was at 56% for the experimental group at 2.9% for the control group. The results indicate the importance of combining pharmacological and psychosocial treatments in patients with schizophrenia, with the ultimate goal of functional recovery. Another study on chronic patients found that in a total sample of 119 patients, 80% had remission and 33% had functional recovery. When pharmacological and psychosocial treatment are combined, the percentage of remission increased to 91% and recovery to 97%.[70]

CONCLUSIONS

The revision of various studies has demonstrated that in patients with schizophrenia, symptomatic remission and functional recovery are possible. According to the studies revised, symptomatic remission occurs in a range between 22% to 97%, and functional recovery between 10% and 68%. Some authors consider it between 10% and 15%, and others indicate that in the 21st century, 50% could recover, with knowledge of the effective roads to recovery, and services with these characteristics being available to patients.[28] Measurement of clinical symptomatic remission can be carried out through different mathematical formulae, using pre-post treatment designs, or even assessing the reduction of these at the level of severity at which they are considered "mild", and with a remission of at least six months' duration. The most important thing for the patient is "to feel alright"; that is, to be in remission for a determined period.[39] Functional recovery is more complex, as it involves the combinations of various clinical and functional factors, as well as an adequate level of psychosocial function, cognitive function, and quality of life for a longer period of duration of at least two years. Multiple elements or dimensions of functional recovery have also been proposed, such as freedom from psychotic symptomatology, productive activities in daily life such as having a job and an income, living independently, and having social relationships.[38] At the time these studies were performed, there evidently did not exist a universal definition of symptomatic remission or functional recovery, the result of which was that each researcher used their own criteria, giving rise to various definitions without the possibility of reaching agreements or drawing comparisons between them.[44] Scientific research indicates that until now there has not been an international consensus with respect to an operational definition of "symptomatic remission" or "functional recovery", and as such, the meaning of these. Nor are there agreements in terms of unified criteria for measuring these phenomena. However, taking into account the wide variety of research in these areas of study, the proposals and advances made have been considerable. It could be concluded that we find ourselves in the process and with the expectation of achieving universal consensus in the future. The need to develop a model that integrates the effectiveness of treatment, the components of the recovery process, and the factors to do with functional recovery has recently been proposed. This would allow a preliminary theory to be prepared around this phenomenon with specific parameters identified such as: initial recovery (fighting disability), partial recovery (living with disability), and total recovery (living beyond disability).[71] Other recent interesting aspects have been: 1) the first publication of a revision of instruments to assess functional recovery,[72] 2) the need to consider and implement psychosocial treatments to promote functional recovery, which implies taking into account the interactions of pharmacological and psychosocial treatments,[73] 3) psychotherapy,[74] and 4) redefining the assessment of functional recovery, which implies the consideration of clinical and psychosocial aspects.[75]

The evidence-based foci which integrate treatment and biopsychosocial rehabilitation have served as instruments to consider "functional recovery" as a viable option in patients with schizophrenia. It is important to mention that the consideration around this concept also stemmed from initiatives proposed by people with schizophrenia who have given testimonies, occasionally in writing, about their expectations around how they have recovered from their illness.[76-79] One testimony indicated that: "the goal of the recovery process is not going back to normal. The goal is about our human vocation of being a deeper and more complete human being."[80] It was therefore the mental health service users and their families who requested and recommended research into various aspects related to "functional recovery" of patients in the community. Because of this, it was considered a success obtained by people with schizophrenia who have managed to achieve satisfactory lives, thereby contributing to the possibility of research in order to have greater knowledge about this area of study.[81] Currently, the pursuit of "symptomatic remission" and "functional recovery" appears as one of the primary objectives in the treatment of, and investigation into, the field of schizophrenia.[82,83] The complexity of this approach is illustrated in figure 2, which notes the diverse components that interact among themselves and which are related with relevant aspects of "functional recovery".[16] The concept of "functional recovery" has been included in mental health policies in countries such as Australia, Ireland, New Zealand, England, and Wales, as well as the United States.[55] A large number of investigations have led to the pro-

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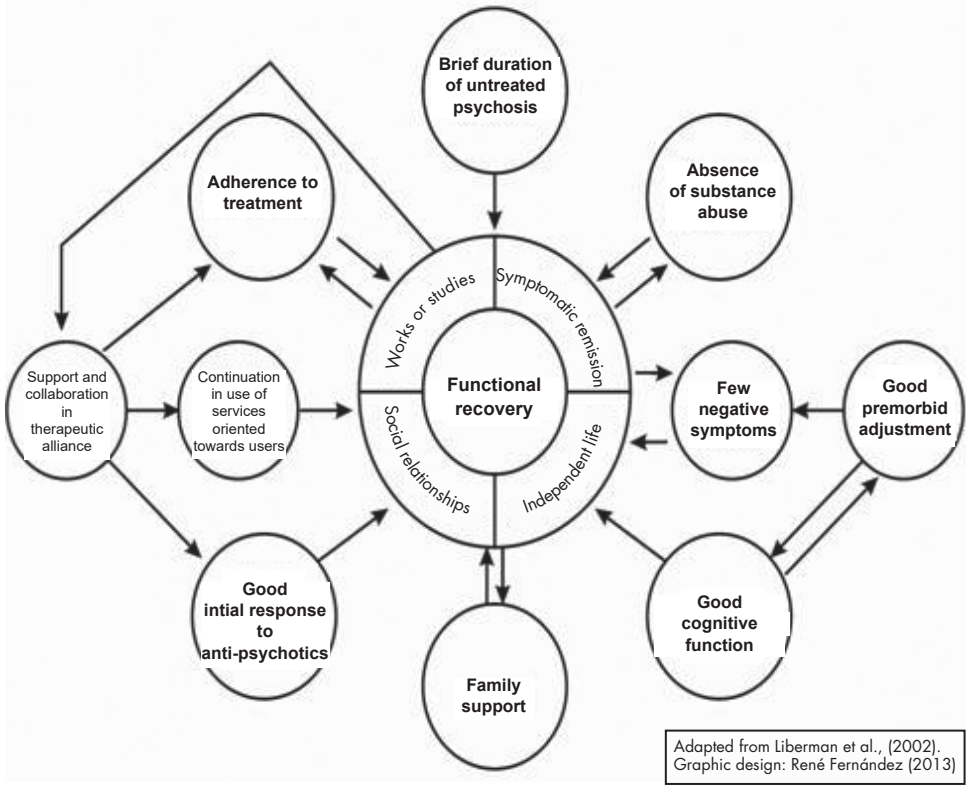

Figure 2. Factors related with aspects of functional recovery in schizophrenia.

posal that mental health services in the near future should be oriented towards achieving functional recovery in patients by means of integrated programs of pharmacological treatment and psychosocial rehabilitation.[54,84-86] New health policies indicate that "mental health care must give equal consideration to "functional recovery" as it does to the symptoms and the illness",[87] and in an equal way to other aspects related to putting recovery strategies into action, such as the reduction of relapses and re-hospitalizations, the treatment of persistent symptoms, the effective use and completion of anti-psychotic medications, obtaining the corresponding social support, and the control of stress, etc.,[88] as well as the wide variety of family interventions that have demonstrated their usefulness in the process of "functional recovery".[89]

The treatment of schizophrenia is undergoing a process of change, with a tendency towards seeking "functional recovery".[86] In this context, it seems important to consider criteria that assess the effectiveness of treatment, taking into account important aspects of the patient's real life in the community. In this regard, various questions have been put forward that clinicians should ask themselves about their patients, such as: has there been a considerable improvement? Is there a treatment that could give them a better quality of life? What could be done to maintain the improvements obtained? Is there the possibility of improving their functional recovery or obtaining better results in another specific aspect of their illness?[75] It is evidently not possible to measure the results of treatment by considering one sole aspect. Due to its complexity, the biopsychosocial model implies the need for various parameters of assessment. We need to know not only if the patient has improved, but also by how much, in what aspects, and for how long. What is evident is that the assessment of comprehensive treatment must include the clinical and the functional components. This area of study is undergoing an internal process of clarification, and as such, it is recommended to complete exhaustive research now, with the aim of achieving consolidation in the future.

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