



Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



SPECIAL ARTICLE

Clinical meaningful outcomes in schizophrenia: remission and recovery

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Received June 28, 2010; accepted December 30, 2010

KEYWORDS

Schizophrenia;
Functional Recovery;
Review;
Empirical Research

Abstract The traditional view of schizophrenia as a disabling and irremediably progressive disease is being reconsidered because of the evidences arising from long-term follow-up studies. On the other hand, recent advances of therapies have yielded significant functional improvements for some patients. Together, these facts are serving to raise treatment prospects, placing the focus on functional recovery. Although the availability of a valid set of consensus remission criteria has been an important step toward the definition of therapeutic objectives and the conceptualization of recovery, remission and recovery still are rare concepts in the setting of routine clinical practice. The present article includes a brief review of these concepts, and presents the results from two observational European studies that provide empirical data about the actual situation of ambulatory patients with schizophrenia in terms of symptomatic remission, and that help in advancing the conceptualization of recovery, contributing to the development of clinical and research definitional criteria. Such results indicate that remission of symptoms constitutes a realistic therapeutic goal in a number of patients, with a considerable temporal stability; on the other hand, recovery definitions should include functional and subjective dimensions. In conclusion, remission is a tenable and clinically valid concept, with a significant contribution to functional improvement. Meanwhile, the recovery construct still requires substantial development.

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PALABRAS CLAVE

Esquizofrenia;
Recuperación
funcional;
Revisión;
Investigación empírica

Resultados clínicos relevantes en esquizofrenia: remisión y recuperación

Resumen La concepción de la esquizofrenia como una enfermedad incapacitante e indefectiblemente progresiva está en proceso de revisión gracias a las evidencias acumuladas en estudios de seguimiento a largo plazo. Los avances en el tratamiento, por otro lado, permiten mejoras funcionales contrastadas en algunos pacientes. Todo ello está provocando un aumento de las expectativas terapéuticas, orientadas hacia la recuperación funcional. Aunque la formulación de unos criterios de remisión consensuados y válidos ha sido un paso importante en la definición de los objetivos del tratamiento y en la conceptualización de la recuperación, los conceptos de remisión y recuperación aún se utilizan poco en el contexto de la práctica clínica habitual.

En el presente artículo se incluye una revisión breve de estos conceptos, y se presentan los resultados de dos estudios observacionales europeos que aportan datos empíricos que permiten conocer cuál es la situación real de los pacientes ambulatorios con esquizofrenia en términos de remisión sintomática y, adicionalmente, avanzar en la conceptualización de la recuperación, lo que contribuye al desarrollo de unos criterios de definición clínicos y de investigación. Según estos resultados, la remisión de síntomas es un objetivo terapéutico realista en un número significativo de pacientes y presenta una estabilidad considerable en el tiempo; por su parte, las definiciones de recuperación deben incluir aspectos funcionales y subjetivos. En conclusión, la remisión es un concepto viable y clínicamente válido, y que favorece notablemente la mejoría funcional; mientras, el concepto de recuperación aún está en proceso de definición.

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Introduction

The concepts of remission and recovery, understood as the disappearance of manifestations of the disease and the socio-vocational rehabilitation of patients, have traditionally been used in non-psychiatric chronic diseases to define treatment goals. In the psychiatry field, the successful application of these concepts in the treatment of mood and anxiety disorders has represented a qualitative leap in terms of their clinical management, and has also encouraged its application in the area of psychotic disorders.

Although the nature and course of psychotic disorders in general, and schizophrenia in particular, differ from those of affective disorders, there has been substantial progress in the last decade, both in establishing the validity of the concept of symptomatic remission and in the development of a conceptual framework on the functional recovery of patients with schizophrenia. If the development of new drugs and modalities of psychosocial services is added to this, we can understand the attitude of therapeutic optimism and the most ambitious attitude in reaching the goals of treatment in recent years. This, of course, has attracted great interest, not only in clinical and research fields, but has transcended to all patients and their families, and beyond, including the health administration that regulates and plans care provision, promoting the development of interventions and models oriented towards rehabilitation, and to the social and vocational reintegration of these patients.

In Europe, the ESFERA (epidemiological study to assess the remission of symptoms and social and vocational

functioning in outpatients with schizophrenia) and SOHO (Schizophrenia Outpatients Health Outcomes) studies were performed under this conceptual framework, investigating clinical outcomes of involved patients over 1 and 3 years, respectively. The authors expose their thoughts about how the concepts of remission and recovery concern the definition of therapeutic goals of schizophrenia, and provide an example on how they were adapted and what results were obtained in the two aforesaid studies¹⁻⁴, in which design they participated. Because these studies provide complementary information, this paper features a joint comment of their results, which was not achievable in their separate publications.

Historical perspective

Despite it was the same Kräpelin who first documented spontaneous remissions in some patients, his seminal description of schizophrenia was that of a chronic and certainly progressive disease for most of patients⁵. Although the posterior definition of the schizophrenia construct advocated by Eugene Bleuler^{6,7} was done from a dynamic perspective, and even before the advent of antipsychotic drugs, the hypothesis of the heterogeneity of the course of this disease had already been defended, such initial conception dominated the nosology of schizophrenia until the last third of the preceding century⁸. It had important practical consequences, including the resignation of clinicians, patients and families who faced inevitable mental and social deterioration, severe stigma, and lack of ambition in the definition of therapeutic goals.

Several prospective epidemiological long-term studies carried out during the past decades showed, however, that symptomatic and social recovery is possible in a substantial proportion of patients after several decades of their initial hospitalization⁹⁻¹⁵; even if these results should be interpreted taking into account the limitations, resulting from the heterogeneity of these investigations as to the populations studied and the criteria used to define their outcomes. More recently, the malleability of the course of schizophrenia was reflected in the three-phase model of the treatment guidelines of the *American Psychiatric Association* (APA), which provides the transition of patients between acute and stable phases, with periods of complete or partial remission¹⁶.

Therapeutic expectations have been reinforced with the arrival of second generation antipsychotics and widespread introduction of psychosocial interventions. Therefore, sustained remission of symptoms is the starting point for achieving functional improvement¹⁷. Thus, we are faced with a paradigm implying a hierarchy of three therapeutic outcomes¹⁸: the *response*, defined as symptom control and relapse prevention; *remission*, characterized by flagrant and sustained disappearance of signs and symptoms; and *recovery*, an outcome asserting social and functional autonomy of patients.

The concepts of remission and recovery in schizophrenia

Background: criteria for remission in mood and anxiety disorders

As in definitions used in non-psychiatric diseases, where a “not measurable” residual state of the disease may allow the patient’s functional recovery, remission in affective disorders was conceptualized not as the total absence of depressive symptoms, but as the presence of symptoms of minimum intensity capable of producing, at the most, a mild functional interference¹⁹. These criteria for remission were proved valid in subsequent prospective studies, demonstrating their relevance compared to the classical concepts of clinical response and stability, and their value to establish a prognosis²⁰⁻²². This success led to the implementation of similar approaches for anguish disorder, generalized anxiety disorder and eating disorders.

Development of criteria for remission in schizophrenia

The enhancement of therapeutic expectations coupled to the relevant role that has been given to remission to define therapeutic goals in psychiatry, triggered the development of a standardized definition of remission for schizophrenia. With this purpose, the Remission in Schizophrenia Working Group was convened in 2003, whose activities culminated in the publication of a set of operational criteria based on distinct thresholds for symptom severity for reaching and maintaining improvement over time²³. Additionally, this definition incorporated an innovative postulate that permits a dimensional approach to the clinical evaluation of

the disease, proposing clusters of symptoms, in contrast to the categorical approach, still in force, in the classification made by the Diagnostic and Statistical Manual of Mental Disorders (DSM) that entails instead the classification of patients. The three dimensions considered are: negative, executive-disorganized, and psychotic, representing related but distinguishable components in the clinical presentation of schizophrenia; they include diagnostic criteria, emphasizing the central role of negative, affective and cognitive symptoms. Currently, the latter issue is one of the novelties in the field of schizophrenia, because of the preponderance traditionally granted to the psychotic symptoms as of the kraepelinian construct of dementia praecox²⁴. By placing them into a set of dimensions, the attainment of good therapeutic outcomes becomes possible without the need for qualitative shifts on patients’ condition²⁵, establishing a parallel to the concept of remission in affective disorders respective to the symptom continuum with normal life experience.

The proposed criteria for remission allow the use of any of the frequently used scales for assessing schizophrenia symptoms: the Scales for the Assessment of Positive Symptoms (SAPS) and negative symptoms (SANS), the Positive and Negative Syndrome Scale (PANSS), or the Brief Psychiatric Rating Scale (BPRS). A selection of items in any of the three options reflects the three dimensions before mentioned, as well as the five diagnostic criteria included in DSM-IV (Table 1). As the remission involves an independent contribution of the three dimensions, the criteria require the score to be mild or inferior (≤ 3 in the case of PANSS or BPRS or ≤ 2 in the case of SAPS-SANS) in all items selected simultaneously. In addition, it is required that this minimum level of symptoms is maintained for at least six months to achieve remission²³.

The formulation of the criteria for remission has been extremely important because it is actually the first formal, standardized definition of a therapeutic target on schizophrenia. Its publication was a shock for clinical research, in such a way that very recent studies have revealed that this operational definition of remission is a more rigorous measurement than clinical stability²⁶⁻³⁰, which is associated with significant functional³¹⁻³³ and cognitive³⁴ improvements, and has good predictive validity on psychopathology³⁵.

The successful validation of these criteria for remission has incentivized the incorporation of this concept to long-term therapeutic targets on schizophrenia. The remission is an ambitious but realistic goal, and may help monitor the progress of the therapeutic process which, in turn, has positive effects on patients, their families and clinicians³⁶. However, these criteria are limited to three dimensions of psychopathology (negative, disorganization and positive), and do not consider other components of the disease that are crucial for an adequate psychosocial functioning¹⁸.

Conceptual development of recovery criteria in schizophrenia

Analogous with the two-phase outcome model in mood and anxiety disorders, the definition of remission excludes functional and cognitive outcomes, whereas remission is

Table 1 Operational criteria for remission in schizophrenia proposed by the Remission in Schizophrenia Working Group with their correspondence and relationship with previous constructs of the pathophysiological dimensions and DSM-IV criteria for schizophrenia

Psychoopathological dimension	DSM-IV Criteria	Operational criteria for remission					
		SAPS-SANS		PANSS		BPRS	
		Criteria	Item	Criteria	Item	Criteria	Item
Psychotic (distortion of reality)	Delusions	Delusions	20 (SAPS)	Delusions	P1	Grandiosity Suspicion	8 11
				Unusual content of thought	G9	Unusual content of thought	15
Disorganized	Hallucinations	Hallucinations	7 (SAPS)	Hallucinatory behavior	P3	Hallucinatory behavior	12
	Disorganized speech	Formal thought disorder	34 (SAPS)	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganized or catatonic behavior	Bizarre behavior	25 (SAPS)	Mannerism and postures	G5	Mannerisms and posturing	7
Negativism (psychomotor poverty)	Negative symptoms	Affective dismay	7 (SANS)	Numbing	N1	Numbing	16
		Abulia-apathy	17 (SANS)	Social withdrawal	N4	No correspondence	
		Anhedonia/ unsociability	22 (SANS)	Lack of spontaneity	N6	No correspondence	
		Alogia	13 (SANS)				

Adapted from Andreasen NC et al.²³, using the terms adopted in the Spanish edition of the fourth revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) and from validated versions of the scales for use in Spain. SAPS: Scale for the Assessment of Positive Symptoms, SANS: Scale for the Assessment of Negative Symptoms, PANSS: Scale for Assessing Positive and Negative Symptoms, BPRS: Brief Psychiatric Rating Scale.

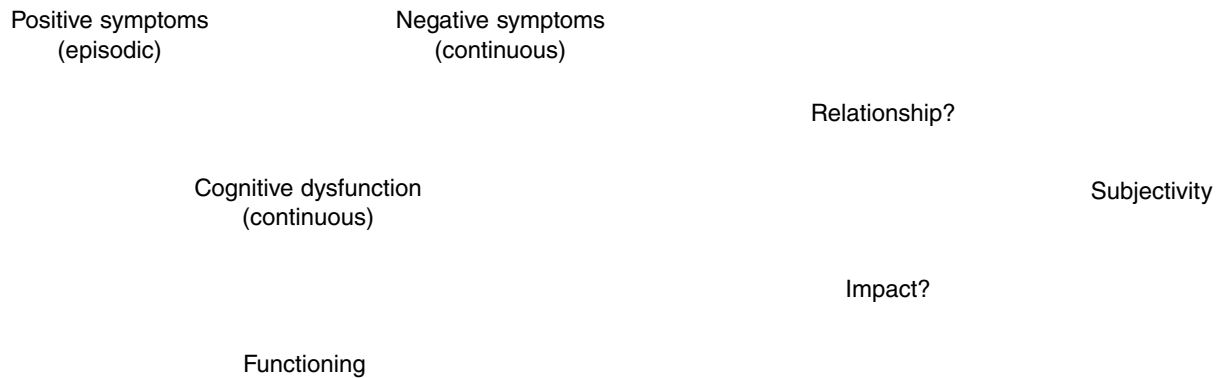


Figure 1 Complex relationships between symptoms, cognition and functionality in schizophrenia. The development of the recovery concept will be possible with the evolving appreciation for the relationship between cognitive and psychosocial dysfunctions and the core symptoms of the disease. Our current knowledge about the long-term outcomes of therapeutic interventions on these dysfunctions and their relationship with the changes of patterns and severity of symptoms is limited. Both, the relationship of psychotic (episodic) with negative (continuous) symptoms, as well as their repercussion on patient's functioning have to be uncovered. On the other hand, the personal subjective elements, related to poorly defined mental conditions, such as hope, empowerment or respect, also have a relevant role in these relationships, but several important issues, including whether they are premises or consequences of recovery, and how to best achieve them in each particular individual, remain elusive.

the basis for achieving functional and cognitive outcomes. This principle is currently guiding the development of the concept of recovery.

Available studies in the literature provide data on the still limited knowledge of long-term course of functional and psychosocial outcomes in patients with schizophrenia, and its relation to changes in the patterns and severity of symptoms^{17,37} (see Figure 1 and the accompanying explanatory text).

Epidemiological studies, already mentioned, used convergent definitions of recovery at a suitable functional or regulatory level, along with other more variable aspects such as social relations or independence³⁸. However, they all fail to sufficiently address the ability of patients to meet the challenges of daily life^{18,39}. We know today that this capability has determining internal (mood symptoms, cognitive deficits) and external (social and vocational reintegration resources, etc.) factors that must be considered and incorporated in recovery definitions⁴⁰.

A proper translation of the construct of recovery in a measurable clinical concept, suitable for research is still missing^{37,39}. The functional outcome measures currently available do not cover all relevant domains and their psychometric properties are not demonstrated⁴¹, so it is necessary to develop new measures focusing on easily observable behaviors, with adequate psychometric validity, covering the whole spectrum of relevant domains, and that are sensitive to the functional impairment of patients with schizophrenia (and to their constraints mentioned above)⁴¹. Moreover, due to the biographical and subjective impact of schizophrenia, and to the influence that cognitive changes may have on patients' subjective experience, it is also necessary that such measures capture the influence of subjective phenomenological elements of the functional outcomes⁴².

Remission and recovery in SOHO and ESFERA studies

Design and Definitions

SOHO and ESFERA studies, funded by Lilly Research Laboratories, were designed to observationally evaluate clinical outcomes in outpatients with schizophrenia and to link them with socio-demographic and clinical variables. Unlike the ESFERA study, the original SOHO protocol did not contemplate the assessment of remission and recovery, but because of the complementarities of their designs (Table 2) and provided the opportunity to evaluate the performance of patients treated in clinical practice, operational definitions of data were proposed and implemented, *a posteriori*, to obtain empirical results for the evaluation of these concepts. The implementation of previously agreed remission criteria and definitions of recovery used, were adapted to the design features and instruments used in each study (Table 2). Thus, the Clinical Global Impression Scale for Schizophrenia (CGI-SCH), successfully validated against the formulation of the criteria for remission based on PANSS⁴³ was used instead of the latter in the SOHO study; and in the ESFERA study, given the transverse nature of its first part, the minimum period of six months (temporary component) of the criteria for remission was not considered. Moreover, due to the long follow-up of the SOHO study (3 years), a thorough and strict definition of recovery was drawn up, trying to reflect the ingredients mentioned in the previous section (remission and adequate functioning, together with the ambitious goal of an appropriate quality of life¹⁸; see Table 2). In the ESFERA study, a holistic approach was applied to define recovery as the optimal level of psychosocial functioning on the basis of remission of symptoms. We used a cutoff >80 points on the

Table 2 Design and objectives of the Schizophrenia Outpatients Health Outcomes (SOHO) study and of the epidemiological study to assess remission of symptoms and social and vocational functioning in outpatients with schizophrenia (ESFERA)

Study	Design	Objectives	Concept and operational criteria	Frequency of remission/ recovery
SOHO ⁵¹ :	<ul style="list-style-type: none"> Observational, prospective, three-year follow-up Outpatients with schizophrenia in routine visit modifying or starting antipsychotic medication Over-sampling to include half of the sample in the cohort of olanzapine 	<p><u>Primary:</u> Relative effectiveness of olanzapine versus other antipsychotics</p> <p><u>Secondary:</u> Relate patterns of use of antipsychotics with health outcomes</p> <p><u>Sub-analysis:</u> Frequency and factors associated with remission Frequency and factors associated with recovery</p>	<p><u>Remission:</u> Score ≤ 3 held for at least 6 months in the following CGI-SCH subscales⁵²: CGI-SCH-global severity CGI-SCH-positive symptoms CGI-SCH-negative symptoms CGI-SCH-cognitive function</p> <p><u>Recovery:</u> Maintenance of the following three criteria for a minimum period of 24 months and until the final study visit: Remission criteria (those mentioned above) Proper functioning (paid job, active student or householder, independent living and maintaining at least one social contact in the last month or living with a partner) Adequate quality of life (the EuroQol-5 Dimensions visual scale scores of ≥ 70)</p>	<p><u>Remission:</u> N = 6516 38.2% during the first year 64.6% during the next 3-yr. follow-up</p> <p><u>Recovery:</u> N = 6642 32.5% remission criteria 12.8% adequate functionality 26.8% adequate Quality of life 4.0% recovery (9.6% among those who were never treated before with antipsychotics)</p>

Study	Design	Objectives	Concept and operational criteria	Frequency of remission/ recovery
ESFERA ⁶² :	<p>Desing</p> <ul style="list-style-type: none"> • Cross section followed by prospectively follow-up of one year • Outpatients with clinically stable schizophrenia routine visit. Monitoring only on patients who met remission criteria in cross-section 	<p>Primary:</p> <ul style="list-style-type: none"> Frequency of remission Frequency of adequate functioning <p>Secondary:</p> <ul style="list-style-type: none"> Factors associated with remission Validity of the construct of remission <p>Subanalyses:</p> <ul style="list-style-type: none"> Frequency and factors associated with recovery 	<p>Remission:</p> <ul style="list-style-type: none"> Criteria from the Working Group for the Remission of Schizophrenia²³ without including the temporary component: score ≤ 2 in the following items of the scale: <ul style="list-style-type: none"> 7. 20, 25 and 34 on the SAPS scale⁵³ (table 1) 7. 13, 17 and 22 on the SANS scale⁵⁴ (see Table 1) 	<p>Remission:</p> <ul style="list-style-type: none"> Baseline (N = 1010) <ul style="list-style-type: none"> 44, 8% in remission Endpoint (N = 376;^a 76 were lost) <ul style="list-style-type: none"> 89, 9% of those in remission at baseline
			<p>Recovery:</p> <ul style="list-style-type: none"> Compliance of the following two criteria during the final assessment of the study: <ul style="list-style-type: none"> Remission criteria (those mentioned above) Total score according to the Global Functioning Evaluation on Functioning >80 	<p>Recovery:</p> <ul style="list-style-type: none"> Baseline (N = 1010) <ul style="list-style-type: none"> 10, 2% in recovery (22, 8% within the remission group) Endpoint (N = 376;^a 76 were lost) <ul style="list-style-type: none"> 27, 1% within the remission subgroup at baseline

CGI-SCH: Clinical Global Impression Scale for Schizophrenia, ESFERA: epidemiological study assessing the remission symptoms and social and vocational functioning of outpatients with schizophrenia, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, SOHO: Schizophrenia Outpatients Health Outcomes.

^a In the ESFERA study, follow-ups were done only in patients who met the criteria for remission in the baseline cross-sectional assessment, thus the endpoint proportions were calculated only in this subgroup.

Global Assessment of Functioning (GAF, Table 2), following the recently proposed notion of functional remission based on achieving minimum levels in a combination of multiple functional domains⁴⁴.

Remission results

In the SOHO study³, of the 6,516 patients evaluated, more than one third met the criteria for remission during the first year, an indicator that doubled during the three follow-up years (Table 2). The factors associated with remission in the regression analysis are presented in Table 3, highlighting that patients more likely to achieve remission were those not previously exposed to antipsychotics, those with better social functioning (stable partner, paid employment and social contacts), and those who were prescribed olanzapine at baseline or during follow-up (Table 5).

At baseline assessment of the ESFERA study², 452 of 1,010 patients (44.8%) met the gravity component of the remission criteria at baseline. After a year, almost 90% of these patients continued to fulfill the remission criteria (Table 2). Among the associated factors, in addition to those already known as the best premorbid adjustment and good attitude toward medication, stands out the positive influence of improvement in depressive symptoms and social cognition during the monitoring year (Table 3).

Recovery results

In the SOHO study⁴, 4.0% of 6,642 evaluated patients met the recovery criteria previously defined, this proportion being more than two-fold greater (10%) among patients who were never treated with antipsychotics before their inclusion (Table 2). According to the regression analysis, those patients with initial good functioning (good socio-labor, living independently) were more likely to meet criteria for recovery during the study. The probability of recovery was also greater in patients with good adherence to treatment (Table 4) and those prescribed olanzapine, clozapine or amisulpiride (Table 5).

In the ESFERA study¹, among the 1,010 evaluated patients in the cross-sectional study, 10.2% met recovery criteria (22.8% within the subgroup in remission), increasing the proportion at the end of the study to 27.1% (Table 2). In addition to other known factors of good prognosis as premorbid adjustment, shorter duration of untreated psychosis, or good attitude towards medication (Table 4), improvement of depressive symptoms and social cognition during follow-up, were associated with higher probability of recovery at the end of the study.

Discussion

From the results obtained in these studies, it is of great interest that in the ESFERA study almost half of a random sample of ambulatory patients with schizophrenia met criteria for remission. On the other hand, the proportion was lower (possibly due to the incorporation of the

temporary component to the criteria) in the SOHO study during the first year, but at the end of the 3-year follow-up, 2 out of 3 patients had reached remission criteria. Together, these results show that remission is a realistic outcome in the setting of the usual clinical practice in Europe. The maintenance of remission criteria in the ESFERA study in 9 out of 10 patients after one year also indicates that remission is a clinical outcome with considerable stability, an aspect of the utmost importance to support the functional improvement of patients.

Consistent with recent research, the data presented support the idea that operationalization of the remission achieved for the criteria reached through consensus, is a clinically valid construct and more relevant than the subjective and heterogeneous assessments on clinical stability²⁶⁻³⁵. In fact, remission was associated with fewer psychotic and affective symptoms and to a smaller number of bad prognosis factors.

It is of great interest to support these two postulates (feasibility and clinical validity), since they were proposed at the time when the remission criteria were being formulated²³. Also, and according to these authors, our data reinforce the idea of a two-phase, non-exclusive, model of treatment outcomes in schizophrenia (remission followed by recovery), in which functional gain might be obtained through sustained remission of symptoms, and that inspired the definitions employed in the ESFERA and SOHO studies.

On the other hand, the proportion of patients who met the recovery criteria was significantly lower in the two studies, especially in the SOHO study. This paper introduced a very strict definition of recovery as it simultaneously required the compliance with the requirements of functionality, sociability and a subjective positive impact measured in terms of quality of life maintained over a period of two years. Additionally, most patients included in SOHO had their antipsychotic treatment modified at baseline, whilst patients had to be clinically stable by the time of their inclusion in the ESFERA study. A positive side, however, is that, according to ESFERA data, the recovery ratio more than doubled among patients who were in remission, compared to the total sample, and was even increased among those who maintained the remission through the final 1-year follow-up. The remission of symptoms alone is not a guarantee of a good psychosocial functioning or of improvement of quality of life of patients with schizophrenia⁴⁵, but maintained remission could allow clinical improvement to translate into significant changes in psychosocial functioning and quality of life⁴⁶.

The association observed between good adherence to treatment and favorable treatment outcomes is already widely known. Additionally, in the SOHO study, the choice of antipsychotic treatment has been shown to have a significant and independent role in achieving recovery. In addition, differences between treatments indicate that individualization and appropriate adjustment of the drugs used, with the prospect of long-term favorable results, is a critical aspect beyond ensuring clinical stability.

The significant relationship between depressive symptoms and functioning observed in the ESFERA study is a relevant issue, even though our current knowledge

Table 3 Factors associated with remission in the Schizophrenia Outpatients Health Outcomes (SOHO) study and the epidemiological study assessing the remission symptoms and social and vocational functioning of outpatients with schizophrenia (ESFERA)

Study	Dependent variable	Factor	OR (IC 95%) ^a
SOHO	Remission over 3-yr. follow-up	Less time since diagnosis (change per year)	1.01 (1.01 – 1.02) ^b
		Lower age at first treatment (change per year)	1.01 (1.00 – 1.01) ^b
		Female (versus male)	1.26 (1.14 – 1.40) ^b
		Beginning of antipsychotic treatment upon inclusion in the study	1.60 (1.33 – 1.93) ^b
		Lower body mass index (per unit change)	1.02 (1.01 – 1.03) ^b
		Stable partner (versus not having)	1.24 (1.11 – 1.38) ^b
		Paid employment (as opposed to not having it)	1.49 (1.32 – 1.69) ^b
		More than one social contact during the previous four weeks (versus not having it)	1.26 (1.13 – 1.40) ^b
		Without treatment with mood stabilizers (against any)	1.39 (1.17 – 1.64) ^b
		Without treatment with anxiolytics or hypnotics (against any)	1.29 (1.16 – 1.43) ^b
		Lower scores on the CGI-SCH scale of overall severity (change per point)	1.32 (1.21 – 1.43) ^b
		Lower scores on the CGI-SCH positive symptoms (change per point)	1.10 (1.05 – 1.15) ^b
		Lower scores on the CGI-SCH scale of negative symptoms (change per point)	1.29 (1.23 – 1.36) ^b
		Lower scores on the CGI-SCH scale of cognitive function (change per point)	1.12 (1.07 – 1.17) ^b
		Less age (change for every five years)	1.10 (1.01 – 1.20) ^b
ESFERA	Remission at baseline	No substance or alcohol abuse (as opposed to having it)	1.49 (1.01 – 2.21) ^b
		Current participation in psychotherapy (as opposed of never being part of it)	1.68 (1.05 – 2.69) ^b
		Participation in psychotherapy in the past (as opposed as never being part of it)	1.60 (1.02 – 2.52) ^b
		Without rehabilitation programs (as opposed to participating in the present)	1.47 (0.98 – 2.22)
		Without rehabilitation programs (as opposed to participating in the past)	1.89 (1.20 – 2.94) ^b
		Best social cognition (change for every 5 points on the GEOPTE scale)	1.57 (1.44 – 1.71) ^b
		Better premorbid adjustment (change per 0.1 points on the PAS scale)	1.39 (1.27 – 1.54) ^b
	Remission at endpoint of 1-yr. Follow-up	No change of antipsychotic treatment during follow-up (versus having them)	2.16 (0.96 – 4.87)
		Better premorbid adjustment (change per 0.1 points on the PAS at baseline)	1.41 (1.09 – 1.86) ^b
		Better attitude toward medication (change for every 5 points on the DAI-10 scale)	1.63 (1.00 – 2.65)
		Improvement on depressive symptoms during follow-up (change for every 5 points on the MADRS scale)	1.62 (1.19 – 2.36) ^b
		Improvement on social cognition during follow-up (change for every 5 points on the GEOPTE scale)	1.75 (1.04 – 2.94) ^b

CGI-SCH: Clinical Global Impression Scale for Schizophrenia, CI: confidence interval, DAI -10: inventory of attitudes toward the medication of 10 items, ESFERA: epidemiological study assessing the remission symptoms and social and vocational functioning of outpatients with schizophrenia, GEOPTE: Spanish Group for Optimization of Treatment of Schizophrenia, MADRS: Montgomery-Asberg Depression Rating Scale, OR: odds ratio, PAS: Premorbid Adjustment Scale Canon-Spoo, SOHO: Schizophrenia Outpatients Health Outcomes.

^a The measures of association (odds ratios) were obtained by binary logistic regression. The factors are expressed in association with the greatest chance for remission. Factors represented the antipsychotic drug in the SOHO study model is presented in Table 5.

^b Significant association.

Table 4 Factors associated with recovery in the Schizophrenia Outpatients Health Outcomes (SOHO) study and the epidemiological study assessing the remission of symptoms and social and vocational functioning on outpatients with schizophrenia (ESFERA).

Study	Dependent variable	Factor	OR (IC 95%) ^a
SOHO	Recovery during follow-up	Less time since diagnosis (change per year)	1.02 (1.00 – 1.03)
		Female (versus male)	1.14 (0.86 – 1.53)
		Paid employment or diligent house chore performance (versus not having it)	8.72 (5.78 – 13.14) ^b
		Living independently (versus not doing it)	7.14 (4.76 – 10.71) ^b
		More than one social contact during the previous four weeks (as opposed to not having it)	1.51 (1.11 – 2.07) ^b
		Initial modification of antipsychotic medication for reasons other than lack of efficacy	1.44 (1.06 – 1.96) ^b
		Good adherence to treatment	2.25 (1.45 – 3.51) ^b
		Lower body mass index (per unit change)	1.05 (1.02 – 1.09) ^b
		Lower scores on the CGI-SCH scale of negative symptoms (exchange for each item)	1.23 (1.10 – 1.38) ^b
		Better attitude toward medication (change for each point in the scale DALI-10)	1.04 (1.01 – 1.08) ^b
ESFERA	Recovery at baseline	Current participation in psychotherapy (as opposed to never being part of it)	1.35 (0.89 – 2.03)
		Participation in psychotherapy in the past (as opposed to never being part of it)	1.61 (1.11 – 2.33) ^b
		Best social cognition (change for every point on the GEOPT scale)	1.07 (1.04 – 1.11) ^b
		Better premorbid adjustment (change per 0.1 points on the PAS scale)	1.41 (1.29 – 1.54) ^b
		Less severe depressive symptoms (per point change in the MADRS scale)	1.10 (1.08 – 1.13) ^b
	Recovery at endpoint of 1-yr. follow-up	Better attitude toward medication (change for each point in the final evaluation. DALI-10 scale)	1.09 (1.01 – 1.16) ^b
		Duration of untreated psychosis (≤ 3 versus > 12 months)	2.28 (1.20 – 4.34) ^b
		Duration of untreated psychosis (3–12 versus > 12 months)	1.63 (0.85 – 3.12)
		ASG monotherapy versus APG monotherapy	1.47 (0.66 – 3.30)
		Monotherapy vs. Antipsychotic combined therapy	4.72 (1.42 – 15.63) ^b
		Better premorbid adjustment (change per 0.1 points on the PAS at baseline)	1.39 (1.18 – 1.64) ^b
		Improvement of depressive symptoms during follow-up (change for every point on the MADRS scale)	1.06 (1.01 – 1.10) ^b
		Improvement of social cognition during follow-up (change for every point on the GEOPT scale)	1.09 (1.02 – 1.17) ^b

CGI-SCH: Clinical Global Impression Scale for Schizophrenia, CI: confidence interval, DALI-10: inventory of attitudes toward the medication of 10 items, ESFERA: epidemiological study assessing the remission symptoms and social and vocational functioning of outpatients with schizophrenia, FGA: first-generation antipsychotics, GEOPT: Spanish Group for Optimization of Treatment of Schizophrenia, MADRS: Montgomery-Asberg Depression Rating Scale, OR: odds ratio, PAS: Premorbid Adjustment Scale Canon-Spoo, SGA: second-generation antipsychotics, SOHO: Schizophrenia Outpatients Health Outcomes.

^a Significant association.

^b The measures of association (odds ratios) were obtained by binary logistic regression. The factors are expressed in association with the greatest chance for recovery. Factors that antipsychotic drug collected in the SOHO study model is presented in Table 5.

Table 5 Factors related to antipsychotic medication associated with remission and recovery in the study Schizophrenia Outpatients Health Outcomes (SOHO)

Dependent variable	Factor (drug/ drug groups)	OR (IC 95%) ^a
Remission over 3-yr. follow-up	Olanzapine	1
	Amisulpiride	0.73 (0.56 – 0.94) ^b
	Clozapine	0.78 (0.65 – 0.95) ^b
	Quetiapine	0.66 (0.56 – 0.77) ^b
	Risperidone	0.74 (0.66 – 0.83) ^b
	Polytherapy	0.64 (0.58 – 0.70) ^b
	Any depot FGA	0.59 (0.51 – 0.69) ^b
	Any oral FGA	0.64 (0.55 – 0.74) ^b
Recovery over 3-yr. follow-up	Olanzapine	1
	Amisulpiride	1.16 (0.51 – 2.65)
	Clozapine	0.43 (0.13 – 1.45)
	Quetiapine	0.20 (0.07 – 0.57) ^b
	Risperidone	0.56 (0.37 – 0.85) ^b
	Polytherapy	0.56 (0.36 – 0.88) ^b
	Any depot FGA	0.30 (0.10 – 0.85) ^b
	Any oral FGA	0.44 (0.21 – 0.94) ^b

CI: confidence interval, FGA: first-generation antipsychotics, OR: odds ratio, SOHO: Schizophrenia Outpatients Health Outcomes.

^aThe measures of association (odds ratios, OR) were calculated using binary logistic regression taking olanzapine as reference.

An odds ratio <1 indicates a lower likelihood of remission or recovery with the concerned drug than with olanzapine.

^b Significant association.

about the relationship between depressive symptoms, remission of the core symptoms of schizophrenia and functioning of patients is still insufficient. However, the finding of the existence of an independent influence on the affective aspects of recovery (as a process) on long-term success, however, is relevant. The recognition of the importance of depressive symptoms on the remission is very recent⁴⁷. In this regard, it should be considered that the improvement of the autonomy of these patients may encounter a complex reality that transcends them. The additional gain of personal competence might avoid the despair and frustration that could lead to a badly-ordered process¹.

The relationship observed in the ESFERA study between the deficits in social cognition and functioning of patients is also interesting. The availability of social skills directly affects the active involvement of patients in their treatment process, and in the efforts to maintain healthy lifestyles and promoting social relations¹. Particularly in the SOHO study, the patients who had previous better social functioning were more likely to achieve remission during follow-up; the ascertainment of an association in this respect serves to underline the desirability of including the idea of the *process* in the conceptualization of the recovery, where the interaction of objective and subjective aspects is relevant to determine the results⁴⁶. This association is consistent with the principle of protection of social networks⁴⁸, by which the integration is not just a good result, but a guarantee of the achievement of autonomy as a final goal, just as the growing recognition of the impact that social cognition deficits have on the functioning of patients with schizophrenia⁴⁹. Regardless of symptomatic remission,

community psychiatry may have a role to provide the required external conditions for recovery. As previously stated, this two-phase model of treatment outcomes is not exclusive, and some models regarded by rehabilitation services see recovery as feasible without the premise of symptomatic remission⁵⁰, but such models are outside the scope of this brief review.

To summarize the contribution of these two studies, we can say that the recovery in schizophrenia should include at least three different areas: remission of symptoms, functional improvement, and subjective response of patients. Remission is feasible and clinically relevant. On the other hand, functional achievements require further development of certain skills, although the final outcome is influenced by other factors, both internal (depressive symptoms) and external (social-work environment), which must be taken into account in the conceptualization of recovery and treatment of patients.

Conclusion

Remission of symptoms in schizophrenia is well conceptualized at present; it can be achieved in a significant proportion of patients, showing considerable stability and great clinical value.

Moreover, remission appears to be a major milestone in achieving better functionality. Maintained remission may, by itself, increase the proportion of patients who can achieve recovery.

The existence of clinical evidence and of specialized literature on the feasibility of recovery in a significant

amount of patients is in contrast with the poor development of the concept of recovery itself. The inclusion of the concept of recovery in investigations such as SOHO and ESFERA studies, and in other recent publications, suggests that only a small proportion of patients may comply with the currently proposed definitions.

Remission of symptoms, functional improvement and subjective response of patients are categories to be included in the definitions of recovery, as outcomes as well as indicators of progress towards achieving the autonomy of patients.

Conflicts of interest

Antonio Ciudad and Inmaculada Gilaberte are full-time employees of Lilly SA.

Julio Bobes has received consulting fees and honoraria from AstraZeneca, Bristol-Myers-Otsuka, GlaxoSmithKline, Janssen-Cilag, Eli Lilly, Pfizer, Sanofi-Aventis and Schering-Plough.

Enric Álvarez has received consulting fees and honoraria from Eli Lilly, Bristol-Myers-Otsuka, Lundbeck, Pfizer, Sanofi-Aventis, Amiral and GlaxoSmithKline.

Luis San has received grant/research support, received honoraria and participated in speakers/advisory boards from AstraZeneca, Bristol-Myers-Squib, Eli Lilly, Pfizer, Janssen and Wyeth.

Acknowledgements

The authors acknowledge the contribution made by Jesus Villoria (medical editor, Medixact, S.L.) for the preparation of this manuscript.

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