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Title: Understanding the impact of persistent symptoms in schizophrenia: cross-sectional findings from the Pattern Study

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Abstract

Background: The high societal burden of schizophrenia is largely caused by the persistence of symptoms and accompanying functional impairment. To date, no studies have specifically assessed the course of persistent symptoms or the individual contributions of positive and negative symptoms to patient functioning. The cross-sectional analysis of the Pattern study provides an international perspective of the burden of schizophrenia.

Methods: Clinically stable outpatients from 140 study centers across eight countries (Argentina, Brazil, Canada, France, Germany, Italy, Spain and the United Kingdom) were assessed using clinical rating scales: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Schizophrenia (CGI-SCH) Scale and the Personal and Social Performance (PSP) Scale. Additional measures included patient-reported outcomes, patient socio-demographic variables, living situation, employment and resource use.

Results: Overall, 1379 patients were assessed and analyzed and had similar sociodemographic characteristics across countries, with 61.6% having persistent positive and/or negative symptoms. Positive and negative symptoms had been persistent for a mean of 9.6 and 8.9 years (SD: 8.8 and 9.6), respectively. Approximately 86% of patients had a functional disability classified as greater than mild. Patients with a higher PANSS Negative Symptom Factor Score were more likely to have a poorer level of functioning.

Conclusions: This analysis examines individual contributions of persistent positive and negative symptoms on patient functioning in different countries. A high prevalence of patients with persistent symptoms and functional impairment was a consistent finding across countries. Longitudinal observations are necessary to assess how to improve persistent symptoms of schizophrenia and overall patient functioning.

ClinicalTrials.gov Identifier: NCT01634542.

Keywords: Schizophrenia, persistent negative symptoms, persistent positive symptoms, epidemiology, quality of life, functional impairment
1. Introduction

Schizophrenia is a severe mental disorder associated with high personal, family and societal burden (Van Os and Kapur, 2009). It is characterized by the presence of a variety of symptoms, which are commonly divided into three main symptom domains: 1) psychotic symptoms such as delusions, hallucinations (reality distortion) and disorganization (thought disorders and bizarre behavior); 2) negative symptoms, which include affective flattening, paucity of thought or speech, lack of motivation and emotional and social withdrawal; and 3) cognitive impairment (especially in memory, attention and executive function) (Liddle, 1987; Malla et al., 1993). The annual incidence of schizophrenia averages 15 per 100,000 and the lifetime prevalence is approximately 1% (Tandon et al., 2008). Schizophrenia is one of the most costly mental disorders in terms of human suffering and societal expenditure. This high burden to patients, their families and wider society is predominantly caused by the persistence of symptoms and occurrence of relapse throughout the course of illness.

A substantial proportion of patients with schizophrenia experience residual and unremitting positive symptoms despite antipsychotic treatment (Suzuki et al., 2012; Suzuki et al., 2011). Approximately 70% of patients treated with antipsychotics show improvement in positive symptoms in the short-term (up to 6 months). However, the response is not consistent or fully effective for all patients (Menezes et al., 2006; Novick et al., 2007; Novick et al., 2009; Van Os and Kapur, 2009). Indeed, it has been estimated that around two-thirds of patients continue to experience significant symptoms two years after treatment initiation, and approximately one-third will continue to experience these symptoms six years after diagnosis (Hegarty et al., 1994; Menezes et al., 2006; Novick et al., 2007; Novick et al., 2009). Insufficiently controlled positive symptoms can lead to poor patient outcomes, including relapse, rehospitalisation, impaired functioning and a reduced quality of life (Norman et al., 1999; Norman et al., 2001; Novick et al., 2009; Csernansky and Schuchart, 2002; Doering et al., 1998; Postrado and Lehman, 1995; Menezes et al., 2006; Novick et al., 2007; Novick et al., 2009; Jordan et al., 2014).

A recent follow-up study of individuals experiencing a first psychotic episode has challenged this negative prognosis. The AESOP-10 study followed up a cohort of 557 people with a first psychotic episode. Of the 126 patients with schizophrenia who were reevaluated about half of them were classified as having a good end state (Morgan et al., 2014). Seventy percent of the cases who were followed up had experienced at least a period of sustained remission. However, these results are somehow in conflict with recent review that found that the proportion of those with schizophrenia who recover on both symptom and functional
outcome is modest (approximately 14%). The discrepancies can be explained by disparities in the patient samples, whether first-episode or not, but also by the lack of consistent definitions of remission and recovery. Recovery should be conceptualized as a multifaceted process, in which symptoms, functioning and patient perception need to be taken into account (McGrath et al., 2014). Recovery obviously depends on remission. Nevertheless, there are a number of other intervening factors affecting recovery that are responsible for the marked variation in outcome observed (Menendez-Miranda et al., 2015; Jordan et al., 2014).

At any point in time, including during the first episode of illness, negative symptoms affect up to 60% of patients with schizophrenia (Bobes et al., 2010), with 30% having primary negative symptoms (Buchanan, 2007; Stahl and Buckley, 2007). Currently available antipsychotics may not have a direct effect on primary negative symptoms (Erhart et al., 2006); therefore, many patients experience persistent negative symptoms even after control of their positive symptoms (Stahl and Grady, 2004; Chue and Lalonde, 2014). The severity of negative symptoms is a predictor of poor patient functioning, also contributing, to a greater extent than positive symptoms, to worse patient outcomes (Fervaha et al., 2014 (a); Fervaha et al., 2014 (b)). Negative symptoms affect the ability of the patient to live independently, perform activities of daily living, engage in social activity, maintain personal relationships and participate in work or study (Rabinowitz et al., 2012; White et al., 2009; Novick et al., 2009). This impact is often evident even within one to two years following treatment of a first episode of illness (Cassidy et al., 2010; Jordan et al., 2014).

Resolution of persistent symptoms is necessary to achieve complete remission and serves to expand patient progress beyond just “stability” and towards improved social and occupational functioning. Furthermore, psychosocial therapies and rehabilitation are most effective when both positive and negative symptoms are effectively controlled (Andreasen et al., 2005). Many patients experience persistent morbidity over the course of their illness and the attainment of remission (defined as a ‘mild or less’ symptom level for the eight core Positive and Negative Syndrome Scale [PANSS] symptoms for at least six consecutive months) remains a significant challenge (Andreasen et al., 2005). A recent literature review of remission in schizophrenia reported that only 45–70% of first-episode and multi-episode patients fulfilled remission criteria at some point during treatment (Lambert et al., 2010).

A number of epidemiological cohort studies have been followed but none has specifically evaluated the natural course of persistent positive and negative symptoms of schizophrenia or compared them between countries (Buchanan, 2007; Chakos et al, 2006; Haro et al., 2003 (a); Haro et al., 2003 (b)). The Pattern study was designed to evaluate the burden and
course of schizophrenia, patient-reported outcomes, healthcare resource utilization and associated costs for patients with persistent symptoms of schizophrenia, not conditioned by any particular therapy or intervention, under standard routine clinical practice. In addition, family members and other informal carers were assessed for their burden and associated costs with caring for these patients. This study is unique in the field of schizophrenia owing to its analysis of the individual contributions of positive and negative persistent symptoms on patient functioning across countries. Whereas previous studies have evaluated the course of illness in patients with schizophrenia by assessing overall symptom burden, the Pattern study examines individual symptom subgroups. The study consists of two phases: a cross-sectional assessment, which forms the baseline observation; and a longitudinal assessment, in order to collect data on all patients who were not in recovery at baseline. The aim of this study is to describe the characteristics of the patients with schizophrenia receiving outpatient treatment in different countries and to examine the relationship between the persistence of different types of symptoms and patient functioning.

2. Materials and methods

2.1 Study design

Pattern is an international, multicenter, non-interventional, prospective, cohort study of schizophrenia patients attending psychiatric outpatient clinics. The study was conducted by psychiatrists treating patients with schizophrenia in outpatient facilities. Recruitment within the sites was based on a sequential selection from patients with a diagnosis of schizophrenia. From a list of current clinic patients generated for each site, those patients without a recent acute relapse, within the last three months according to the treating psychiatrist, were deemed eligible and invited to participate in the study. Patient care and treatment followed routine local clinical practice and was at the discretion of the treating clinician. In addition, family members and other informal carers were invited to participate in the study and were assessed for their burden and associated costs with caring for these patients. The protocol and consent procedures were approved by all local Institute Review Boards/Ethics Committees before study initiation.

2.2 Participants

Adult schizophrenia patients who were treated at psychiatric outpatient clinics were eligible for study entry. To maximize generalizability of study results to the whole population of clinically stable schizophrenia patients, minimal entry criteria were applied regardless of treatment history, comorbidity or history of substance abuse. Participants were at least 18 years old and met criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision or International Classification of Mental Disorders.
Diseases, 10th Revision, documented with an abridged version of the Mini International Neuropsychiatric Inventory, of ≥ 12 months duration before the baseline observation. Family members and other informal carers were invited to participate in the study and respond to questionnaires. All patients and available family members and other informal carers were required to demonstrate ability and willingness to comply with the study protocol and provide informed consent. Exclusion criteria included: an acute psychotic exacerbation in the three months prior to baseline (e.g., hospitalization or increased psychiatric care in order to avoid hospitalization), enrolment in an interventional study at baseline and an inability or unwillingness to comply with the study protocol.

2.3 Patient assessment
Psychiatrists or appropriately trained professionals, patients and their family members or informal carers utilized an electronic hand-held tablet to capture all clinical assessment and patient-reported outcome (PRO) data. Psychiatrists captured data as assessed by clinical rating scales, whilst patients captured PRO questionnaire data independently at the clinic. To ensure instrument validity, PRO questionnaires were administered prior to the completion of other study assessments. At each outpatient attendance, approximately every 3 months for a year, patients were assessed using several clinical rating scales, which included: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Schizophrenia (CGI-SCH) Scale and the PSP Scale. Participating psychiatrists were provided with training in the use of the questionnaires and rating was not blinded since no defined intervention was evaluated. PRO data were assessed by patients using the Schizophrenia Quality of Life Scale (SQLS) at each observation, the Short Form-36 (SF-36) at baseline and at one year and the EuroQol-5 Dimension (EQ-5D) questionnaire at approximately six month intervals (Table 1). Information on patient socio-demographics, living situation, employment, health service use and medical resource use was collected at each visit using the Client Socioeconomic and Services Receipt Inventory (CCSRI). Additional assessment tools included the caregiver’s Clinical Global Impression of change (CGI-Caregiver) and the Schizophrenia Caregiver Questionnaire (SCQ). In all cases, the available validated translated instruments were used. Whilst there is currently no consensus as to the operational criteria and definition of recovery in schizophrenia, previous literature has indicated that measures should be multidimensional and include clinical remission (maintained over a 6-month period) and social outcomes (Emsley, 2011; Andreasen, 2005). As such, recovery was defined per-protocol as PANSS Positive Symptom Factor Score <28, PANSS Negative Symptom Factor Score <20 and Personal and Social Performance (PSP) score ≥80 for at least the previous 6 months.
2.4 Statistical analysis

The primary population for the present analysis, the Cross-Sectional Patient Analysis Set (CS-PAS), consists of all patients who fulfilled all the eligibility criteria for the cross-sectional phase, which included patients with persistent symptoms, those in symptomatic remission or those in recovery but not those with a psychotic exacerbation in the last three months. Psychotic exacerbation was defined as hospitalisation for schizophrenia-related reasons or increased psychiatric care in order to avoid hospitalisation, as judged by the psychiatrist. Descriptive statistics are provided for all variables of interest. Selected data are presented by country or according to the time since first treatment for schizophrenia (≤ 5 years and > 5 years). Based on the ratings of the positive and negative dimensions of the PANSS and the PSP scales, patients were classified into the following non-overlapping symptom groups: predominantly negative persistent symptoms; sub-optimally controlled positive persistent symptoms; and symptomatic remission with poor level of functioning and recovery. Predominantly negative persistent symptoms was defined as a PANSS negative symptoms factor score (NSFS) >20 and PANSS positive symptoms factor score (PSFS) <28; sub-optimally controlled positive persistent symptoms was defined as a PANSS PSFS >28 (irrespective of PANSS NSFS score); symptomatic remission with poor level of functioning corresponded with PANSS PSFS ≤28, PANSS NSFS ≤20 and PSP <80; and recovery, as stated above, was characterized as PANSS PSFS <28, PANSS NSFS <20 and PSP ≥80 for at least the previous 6 months. The PANSS NSFS consists of seven PANSS items: Five ‘negative symptoms’ (blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal and lack of spontaneity and flow of conversation) and two ‘general psychopathology’ items (motor retardation and active social avoidance). The PANSS PSFS consists of eight PANSS items: Five ‘positive symptoms’ (delusions, hallucinatory behaviour, grandiosity, suspiciousness and stereotyped thinking) and three ‘general psychopathology’ items (somatic concern, unusual thought content and lack of judgement and insight) (Marder and Davis, 1997).

Confidence intervals for the estimated multinomial proportions were calculated according to a method proposed by Sison and Glaz (Sison and Glaz, 1995). The relationships between numeric variables, such as the PSP total score and the PANSS NSFS, were assessed based on Spearman’s rank correlation analysis. The Kruskal–Wallis test was used to assess the relationship between PANSS score and the PSP-based function category. Analysis of covariance was used to assess the relationship of PSP with additional variables including the duration of illness and the country. The sample size of this study was based upon feasibility considerations.
3. Results

3.1 Patient characteristics
A total of 1433 patients were recruited into the Pattern study, from 140 study sites in eight countries (Argentina, Brazil, Canada, France, Germany, Italy, Spain and the United Kingdom). Overall, 1379 patients were included in the CS-PAS; 54 (3.8%) patients were excluded, the majority because they did not have a diagnosis of schizophrenia (primarily schizoaffective disorders). Socio-demographic information was similar across the eight countries (Table 2). Overall, patients were predominantly male (71%), with an average age of 42.1 years (standard deviation [SD]: 11.5; range: 18–82). Most patients were either single or unmarried (76.9%) and 27.2% had an informal carer. With regards to employment, only 11.7% of patients were employed; 5.7% reported being in sheltered employment and 2.2% in voluntary/unpaid employment. The most frequent co-morbidities reported by clinicians were: current or past substance abuse (35%); another mental disorder (14%); vascular disease (7.8%); gastrointestinal disorders (7.5%); and metabolic disorders (7.5%).

3.2 Persistence of symptoms
The majority of patients (n=823, 61.6%) had either predominant sub-optimally controlled positive symptoms (PANSS Positive Symptom Factor Score>28) or predominant persistent negative symptoms (PANSS Negative Symptom Factor Score>20), the latter being the most common overall disease state (n=541, 40.5% of patients). The rest of the patients were in symptomatic remission with poor level of functioning (n=469, 35.1%) or recovery (n=43). The mean duration of persistent positive and negative symptoms, regardless of level of severity, was 9.6 (SD: 8.8) and 8.9 (SD 9.6) years, respectively, as reported by the study psychiatrist. In the previous year, 21% of patients were identified as being treatment resistant by their psychiatrist. Antipsychotics were used by 98% of patients and 31% of patients were on combination regimens (54% if drugs from other classes used for the same indication are considered, such as benzodiazepines or antidepressants). Clozapine was the most frequently prescribed antipsychotic (29% of patients, with figures ranging from 16% in France to 72% in Brazil) followed by risperidone (22%), olanzapine (16%) and aripiprazole (15%).

3.3 Severity of disease
Based on clinical ratings scales, most patients were experiencing moderately severe illness (Table 3). More than 86% of patients experienced a degree of functional disability classified
as greater than mild on the PSP scale (13% classified as patient requiring intensive support and supervision and 74% varying degree of disability), with only 13% of the patients experiencing mild difficulties. The duration of illness did not influence the level of functioning substantially. Patients with a higher PANSS NSFS were more likely to have worse level of functioning, as assessed by the PSP scale. A relationship with the PANSS PSFS was present but less pronounced. These effects were consistent across countries (Figures 1a/b).

4. Discussion
The cross-national characteristics of the Pattern study allowed comparison of various patient characteristics and outcome variables between countries, similar to recent investigations into psychopathological characteristics of patients with schizophrenia from Brazil, China and the US (Stefanovics et al., 2014). The data of more than 1300 patients and their family members or informal carers represent a valuable epidemiological contribution towards the study of schizophrenia. Clinically stable patients with a diverse range and severity of symptoms of schizophrenia were observed, and the majority of these patients (61.6%) were identified as having persistent positive and/or negative symptoms. This is consistent with previous studies in schizophrenia, which show that persistent symptoms are prevalent during the course of illness (Buchanan, 2007; Caspi et al., 2004; Hegarty et al., 1994; Menezes et al., 2006; Novick et al., 2007; Novick et al., 2009; Robinson et al., 2004; Van Os and Kapur, 2009).

The patient characteristics observed here are similar to those observed in other outpatient studies of schizophrenia (Smith et al., 2006; Haro et al., 2003 (a)). Approximately, two thirds of the patients were male and mean age was around 42 years. Relevant differences appeared when comparing the living conditions across countries: in Canada, France, German and the UK a low proportion of patients were living with their parents and other members of their family of origin, while in Brazil, Italy and Spain the figures were two or three times higher. Cultural differences are probably underlying these differences (Sartorius et al., 1986; Brekke and Barrio, 1997). In these later countries the roles of families instead of formal services is much more important in taking care of patients with schizophrenia (Magliano et al., 2000).

The level of impairment is very high, with twelve percent of patients having paid employment and ten percent of the patients being married. Previous research assessing patient functioning has generally focused on most developed countries (Marwaha et al., 2007, Marwaha and Johnson, 2004). Here we observe regional variations using a similar methodology. Canada, Germany and Italy have higher frequency of employment.
Employment policies for people with disabilities across countries may explain these differences.

Notably, Pattern is one of the largest cohort studies to specifically investigate the independent contribution of negative symptoms to patient functioning. Previous studies have utilized PANSS total scores and the Schizophrenia Clinical Global Impressions-Severity and -Improvement scales to investigate the severity of symptoms in relation to patient outcomes (Bobes et al., 2010; Chue and Lalonde, 2014; Novick et al., 2007; Novick et al., 2009). In this study, both positive and negative persistent symptoms are clearly measured, showing the relative contribution of each to patient functioning. As a result, these data represent a valuable contribution to the field highlighting the need for future strategies for treating individual symptom subgroups, specifically negative symptoms, and thereby improving overall patient outcomes.

There were some differences in patient's clinical severity and functioning across countries. For example, the PANSS PSFS ranged from 17 in Germany to 27 in Argentina. More striking is the variability in the difference between PANSS PSFS and NSFS: in Argentina and UK the PSFS is higher (Argentina, UK) while in France, Germany, Italy and Spain the NSFS is higher. However, in all cases except the UK, the CGI-SCH negative symptoms score is higher than the CGI-SCH positive symptoms score. Patients in the UK, Germany and Argentina had a higher proportion of patients with mild difficulties in the PSP.

As expected, the range of therapy received varied broadly, especially between regions. Clozapine was the most frequently used treatment overall, although there were substantial differences in its prescription between countries. This variation in rate of prescription of clozapine between countries is consistent with previous studies, which have shown significant differences across countries, as well as across regions and hospitals. A comparison among hospitals showed that the percentages of patients who received clozapine varied from 5.7% to 16.8%, with a national average of 10.5% (Nielsen et al., 2012; Latimer et al., 2013). The causes of such varied clozapine use have not been thoroughly investigated (Nielsen et al., 2012), although variability in overall rates and changes in prescription rates over time suggest that factors other than psychopharmacological principles play an important role in determining the prescription of clozapine in schizophrenia (Xiang et al., 2011). It has been speculated that the observed differences in clozapine prescription may be due to varied treatment resistance within different populations or psychiatrists’ practice patterns, or a combination of both. Furthermore, it is likely that
availability of, and access to, medical resources, and cost considerations, also contributes to this variation.

Persistence of positive and negative symptoms was associated with impaired functional outcomes overall, with severity of negative symptoms more likely than positive symptoms to be associated with compromised patient functioning than positive symptoms (Figure 1). Indeed, recent evidence suggests that persistent symptoms are a stronger predictor of functional outcome than cognitive deficits in both chronically ill and recent-onset patients (Norman et al., 1999; Malla et al., 2002; Jordan et al., 2014). The evidence that symptom remission contributes a much larger variation in functional outcome comes from studies designed to include both symptoms and cognition and controlled for other potential predictors of functional outcome (Norman et al., 1999; Malla et al., 2002; Cassidy et al., 2010). On the other hand evidence for cognition being a strong predictor have either not included symptoms or included symptoms at baseline which would obviously not show any role as it is residual symptoms that are important, especially negative symptoms (Cohen et al., 2006). Our results also replicate previous research, which demonstrated that negative symptoms account for much of the long-term morbidity and poor functional outcomes of patients with schizophrenia (Fervaha et al., 2014 (a); Buchanan, 2007). Of note, the relationship between PANSS score and level of functioning was stronger for negative symptoms compared with positive, which may emphasise the greater importance of negative symptoms to overall patient functioning. The results from this study therefore further substantiate the negative impact of persistent symptoms on the lives of patients with schizophrenia, endorsing the need for treatment strategies that aim to minimize both positive and negative symptoms, improving daily functioning and associated quality of life.

A number of potential limitations of this study should be acknowledged. Only patients in the outpatient setting were recruited; however, patients with persistent symptoms, and often those with the most severe symptoms, may be living in institutions, depending on the country (Uggerby et al., 2011). By contrast, patients with only minimal symptoms may not visit outpatient clinics, making an estimate of the prevalence of persistent symptoms in the overall population of patients with schizophrenia difficult. Patients meeting the protocol-defined criteria of recovery were not included in the longitudinal phase of the study, and this may have introduced a bias whereby such patients were under-recruited at baseline. However, given that the study specific determination of patients in recovery was based on a combination of pre-specified cut-off values on the PANSS PSFS and NSFS, and the PSP assessment, disease status could not have been judged conclusively prior to assessment, minimizing the contribution of this bias. Furthermore, the definition of recovery used may
have limited content validity. Whilst there is currently no consensus as to the operational definition of recovery in schizophrenia, the definition used is multidimensional and includes clinical remission and social outcomes (Emsley et al., 2011; Andreasen et al., 2005). However, it does not take into account a patient’s subjective sense of recovery, quality of life, occupational functioning and cognitive status, which has become increasingly important in the recent literature (Lambert et al., 2010; Emsley et al., 2011; Leucht, 2014). Participating psychiatrists were provided with basic training in the use of the questionnaires; however, inter-rater agreement was not assessed, as the intention of Pattern was to collect real-world data via a non-interventional study design. Finally, since one of the inclusion criteria was that all patients and family members and other informal carers were required to demonstrate willingness to comply with the study protocol and provide informed consent the study may have included mostly adherent patients.

5. Conclusion
This cross-sectional study of 1379 patients, and their carers represents a valuable real-world contribution to the study of schizophrenia, particularly given that naturalistic data from 140 centers across eight countries were collected. Based on this cross-sectional assessment, there was a high prevalence of patients with positive and/or negative persistent symptoms of schizophrenia and associated functional impairment. These results further substantiate the deleterious impact of persistent symptoms, particularly the impact of negative symptoms, on patients’ level of functioning. To date this non-interventional study is the largest to look at the severity of symptoms in schizophrenia using the PANSS Negative and Positive Symptom Factor scores as an independent contributing factors to the disability of schizophrenia.
References


Cohen A.S., Forbes C.B., Mann M.C., Blanchard J.J., 2006. Specific cognitive deficits and differential domains of social functioning impairment in schizophrenia. Schizophr Res. 81, 227-38


Table 1. Assessment tools and time of data collection during the study
(performed in parallel with routinely scheduled clinic appointments)

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Time of data collection</th>
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<tr>
<td>Clinical rating scales</td>
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<tr>
<td>Positive and Negative Syndrome Scale (PANSS)</td>
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<tr>
<td>Clinical Global Impression-Schizophrenia (CGI-SCH) scale</td>
<td>Baseline, 3, 6, 9, 12, 18 and 24 months</td>
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<td>Personal and Social Performance (PSP) scale</td>
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<tr>
<td>Schizophrenia Quality Life Scale (SQLS)</td>
<td>Baseline, 3, 6, 9, 12, 18 and 24 months</td>
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<td>Short Form-36 (SF-36)</td>
<td>Baseline, 12 and 24 months</td>
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<td>EuroQol-5 Dimension (EQ-5D) questionnaire</td>
<td>Baseline and 6, 12, 18 and 24 months</td>
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<td>Socio-demographics &amp; resource use</td>
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<td>Client Socioeconomic and Services Receipt Inventory (CCSRI)</td>
<td>Baseline, 3, 6, 9, 12, 18 and 24 months</td>
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<td>Caregiver outcomes</td>
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<td>Schizophrenia Caregiver Questionnaire (SCQ)</td>
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<td>Caregiver’s Clinical Global Impression scale (CGI-Caregiver)</td>
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<td>Caregiver SF-36</td>
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Table 2. Demographic and baseline characteristics

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<td>89 (76.1)</td>
<td>Unknown*</td>
<td>120 (48.0)</td>
<td>217 (99.1)</td>
<td>189 (91.3)</td>
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<td>937 (67.9)</td>
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<td><strong>Marital status, n (%)</strong></td>
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<tr>
<td>Single/unmarried</td>
<td>87 (79.1)</td>
<td>88 (88.0)</td>
<td>85 (72.6)</td>
<td>182 (76.8)</td>
<td>153 (61.2)</td>
<td>182 (83.1)</td>
<td>173 (83.6)</td>
<td>111 (79.9)</td>
<td>1061 (76.9)</td>
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<td>29 (12.2)</td>
<td>43 (17.2)</td>
<td>19 (8.7)</td>
<td>17 (8.2)</td>
<td>9 (6.5)</td>
<td>141 (10.2)</td>
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<td>Separated</td>
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<tr>
<td>Living conditions, n (%)</td>
<td>21 (19.1)</td>
<td>5 (5.0)</td>
<td>44 (37.6)</td>
<td>115 (48.5)</td>
<td>114 (45.6)</td>
<td>33 (15.1)</td>
<td>35 (16.9)</td>
<td>80 (57.6)</td>
<td>453 (32.8)</td>
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<tr>
<td>-------------------------</td>
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<td>----------</td>
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</tr>
<tr>
<td>Living alone (+/- children)</td>
<td>27 (24.5)</td>
<td>5 (5.0)</td>
<td>44 (37.6)</td>
<td>115 (48.5)</td>
<td>114 (45.6)</td>
<td>33 (15.1)</td>
<td>35 (16.9)</td>
<td>80 (57.6)</td>
<td>453 (32.8)</td>
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<tr>
<td>With spouse/partner (+/- children)</td>
<td>9 (8.2)</td>
<td>4 (4.0)</td>
<td>14 (12.0)</td>
<td>35 (14.8)</td>
<td>59 (23.6)</td>
<td>21 (9.6)</td>
<td>27 (13.0)</td>
<td>14 (10.1)</td>
<td>183 (13.3)</td>
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<td>With parents</td>
<td>40 (36.4)</td>
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<td>63 (26.6)</td>
<td>29 (11.6)</td>
<td>114 (52.1)</td>
<td>104 (50.2)</td>
<td>26 (18.7)</td>
<td>480 (34.8)</td>
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<td>With other relatives</td>
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<td>15 (15.0)</td>
<td>7 (6.0)</td>
<td>12 (5.1)</td>
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<td>16 (7.3)</td>
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<td>3 (2.2)</td>
<td>84 (6.1)</td>
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<td>Living with others/assisted living</td>
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<td>8 (3.4)</td>
<td>41 (16.4)</td>
<td>33 (15.1)</td>
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<td>16 (11.5)</td>
<td>165 (12.0)</td>
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<tr>
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<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
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<th>0.9</th>
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<td>Employed</td>
<td>11 (10.0)</td>
<td>5 (5.0)</td>
<td>18 (15.4)</td>
<td>35 (14.8)</td>
<td>40 (16.0)</td>
<td>31 (14.2)</td>
<td>13 (6.3)</td>
<td>8 (5.8)</td>
<td>161 (11.7)</td>
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<td>Voluntary/unpaid</td>
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<td>0</td>
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<td>18 (12.9)</td>
<td>30 (2.2)</td>
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<td>Sheltered employment</td>
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<td>1 (1.0)</td>
<td>3 (2.6)</td>
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<td>0</td>
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<td>Unemployed</td>
<td>71 (64.5)</td>
<td>46 (46.0)</td>
<td>55 (47.0)</td>
<td>97 (40.9)</td>
<td>26 (10.4)</td>
<td>62 (28.3)</td>
<td>45 (21.7)</td>
<td>94 (67.6)</td>
<td>496 (36.0)</td>
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<tr>
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<td>5 (5.0)</td>
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<td>48 (3.5)</td>
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<td>Housewife/husband</td>
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<td>0</td>
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<td>10 (4.6)</td>
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<td>0</td>
<td>40 (2.9)</td>
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<tr>
<td>Retired/pension</td>
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<td>21 (21.0)</td>
<td>7 (6.0)</td>
<td>18 (7.6)</td>
<td>100 (40.0)</td>
<td>72 (32.9)</td>
<td>58 (28.0)</td>
<td>8 (5.8)</td>
<td>289 (21.0)</td>
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<td>Other</td>
<td>8 (7.3)</td>
<td>18 (18.0)</td>
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<td>63 (26.6)</td>
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<td>27 (12.3)</td>
<td>64 (30.9)</td>
<td>7 (5.0)</td>
<td>228 (16.5)</td>
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<th>Patients with a caregiver, n (%)</th>
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<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
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<td>0</td>
<td>1 (0.9)</td>
<td>0</td>
<td>2 (1.7)</td>
<td>10 (4.2)</td>
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<td>10 (7.2)</td>
<td>30 (2.2)</td>
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<tr>
<td>1</td>
<td>72 (65.5)</td>
<td>74 (74.0)</td>
<td>75 (64.1)</td>
<td>169 (71.3)</td>
<td>165 (66.0)</td>
<td>151 (68.9)</td>
<td>113 (54.6)</td>
<td>101 (72.7)</td>
<td>920 (66.7)</td>
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<tr>
<td>&gt;1</td>
<td>29 (26.4)</td>
<td>26 (26.0)</td>
<td>40 (34.2)</td>
<td>58 (24.5)</td>
<td>83 (33.2)</td>
<td>67 (30.6)</td>
<td>90 (43.5)</td>
<td>28 (20.1)</td>
<td>429 (31.1)</td>
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Patient analysis set.
SD=standard deviation.
*Local laws prevented full collection of these data
<table>
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<th></th>
<th>Argentina</th>
<th>Brazil</th>
<th>Canada</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
<th>Overall</th>
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<td><strong>PANSS, mean (SD)</strong></td>
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<tr>
<td><strong>N</strong></td>
<td>109</td>
<td>100</td>
<td>117</td>
<td>236</td>
<td>249</td>
<td>217</td>
<td>206</td>
<td>139</td>
<td>1373</td>
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<tr>
<td>Positive Symptom Factor Score</td>
<td>26.8 (5.37)</td>
<td>20.7 (7.12)</td>
<td>20.3 (7.03)</td>
<td>18.4 (5.66)</td>
<td>17.3 (7.37)</td>
<td>23.8 (8.38)</td>
<td>22.5 (7.66)</td>
<td>22.9 (9.35)</td>
<td>21.1 (7.89)</td>
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<tr>
<td>Negative Symptom Factor Score</td>
<td>25.1 (5.20)</td>
<td>23.5 (4.90)</td>
<td>20.4 (5.75)</td>
<td>20.4 (6.38)</td>
<td>20.8 (6.89)</td>
<td>26.7 (8.01)</td>
<td>24.4 (7.48)</td>
<td>18.9 (8.62)</td>
<td>22.5 (7.42)</td>
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|                  |           |        |        |        |         |       |       |          |         |
| **CGI-SCH, mean (SD)** |           |        |        |        |         |       |       |          |         |
| **N**            | 109       | 100    | 117    | 237    | 249     | 217   | 206   | 139      | 1374    |
| Positive symptoms | 3.7 (1.16) | 3.3 (1.28) | 3.2 (1.33) | 3.3 (1.28) | 2.6 (1.31) | 3.6 (1.33) | 3.4 (1.35) | 3.5 (1.37) | 3.3 (1.35) |
| Negative symptoms | 4.2 (0.86) | 4.1 (0.92) | 3.5 (0.92) | 3.9 (1.15) | 3.8 (1.07) | 4.3 (1.12) | 4.2 (1.07) | 3.3 (1.41) | 3.9 (1.14) |
| Depressive symptoms | 2.6 (1.00) | 1.9 (0.98) | 1.8 (0.94) | 2.0 (1.19) | 2.5 (1.22) | 2.9 (1.26) | 2.6 (1.11) | 2.4 (1.31) | 2.4 (1.21) |
| Cognitive symptoms | 3.8 (1.08) | 3.7 (1.09) | 2.8 (1.07) | 3.2 (1.28) | 3.3 (1.09) | 3.6 (1.15) | 3.5 (1.07) | 2.7 (1.28) | 3.3 (1.20) |
| Overall severity  | 4.3 (0.74) | 4.2 (0.96) | 3.5 (1.01) | 3.8 (0.97) | 3.7 (0.99) | 4.2 (0.96) | 4.1 (1.03) | 3.6 (1.26) | 3.9 (1.03) |

|                  |           |        |        |        |         |       |       |          |         |
| **PSP Scale, n (%)** |           |        |        |        |         |       |       |          |         |
| **N**            | 109       | 100    | 117    | 237    | 249     | 217   | 206   | 139      | 1374    |
| Mild difficulties | 18 (16.5) | 6 (6.0) | 8 (6.8) | 27 (11.4) | 45 (18.1) | 20 (9.2) | 17 (8.3) | 40 (28.8) | 181 (13.2) |
| Varying degree of disability | 89 (81.7) | 83 (83.0) | 106 (90.6) | 177 (74.7) | 166 (66.7) | 150 (69.1) | 165 (80.1) | 82 (59.0) | 1018 (74.1) |
| Patient requires intense support/supervision | 2 (1.8) | 11 (11.0) | 3 (2.6) | 33 (13.9) | 38 (15.3) | 47 (21.7) | 24 (11.7) | 17 (12.2) | 175 (12.7) |

Patient analysis set.
PSP total score-based categories: Mild difficulties: 71–100; Varying degrees of disability: 31–70; Intensive support/supervision: 0–30.
PANSS=Positive and Negative Syndrome Scale; CGI-SCH= Clinical Global Impression-Schizophrenia Scale; PSP= Personal and Social Performance