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# 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 sociodemographic 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.


## 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, 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

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et al., 2007, 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, 2009). Insufficiently controlled positive symptoms can lead to poor patient outcomes, including relapse, rehospitalization, impaired functioning and a reduced quality of life (Norman et al., 1999, 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, 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. (2014a,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., 2003a; Haro et al., 2003b). 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 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

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