

# Schizophrenia Outpatient Health Outcomes study: twelve-month findings

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**Background:** The purpose of this study was to assess the 12-month outcomes associated with naturalistic antipsychotic treatment of patients participating in the Schizophrenia Outpatient Health Outcomes (SOHO) study.

**Methods:** SOHO is a 3-year, prospective, observational study of the health outcomes associated with antipsychotic treatment in 10 European countries. The study included over 10,000 outpatients who were initiating or changing their antipsychotic medication. Medication use pattern, change in symptom severity, social functioning, and health-related quality of life were assessed, as well as rates of response, remission, treatment discontinuation, adverse events, and hospitalization.

**Results:** Clinical Global Impression-Severity for Schizophrenia (CGI-SCH) and quality of life scores improved in all treatment cohorts. There were greater improvements in the CGI-SCH overall symptom score and in the CGI-SCH positive, negative, cognitive, and depressive symptom scores in the olanzapine and clozapine cohorts compared with other treatment cohorts. Changes were associated with an improvement in quality of life. Patients treated with olanzapine, quetiapine, and clozapine had better tolerability per extrapyramidal symptoms and sexual-related dysfunction measures compared with patients receiving risperidone, amisulpride, or typicals. Patients treated with olanzapine had greater weight gain than patients in all other treatment cohorts.

**Conclusion:** Patients initiated on olanzapine and clozapine tend to have better outcomes at 12 months than patients initiated on other antipsychotics in routine outpatient clinical practice. Results should be interpreted conservatively due to the nonrandomized study design.

**Keywords:** schizophrenia, treatment, outcomes, outpatient, remission, antipsychotics

## Introduction

Although antipsychotics remain the cornerstone of the treatment of schizophrenia, the relative effectiveness of different antipsychotics in routine clinical practice is still a topic of debate. Most of the current knowledge about the effects of antipsychotic drugs originates from randomized clinical trials, which have formed the evidence base for current expert guidelines and recommendations for the treatment of schizophrenia.<sup>1-4</sup> However, randomized clinical trials have inherent design limitations and cannot fully reflect the use and impact of antipsychotic medications in actual clinical practice. Most randomized clinical trials are of short duration,<sup>5</sup> involve selected samples of patients,<sup>6,7</sup> focus on clinical outcomes instead of quality of life or social functioning,<sup>8</sup> and impose stringent treatment regimens that limit the generalizability of the results.<sup>9-11</sup>

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Recent meta-analyses of randomized clinical trials comparing the effects of antipsychotics<sup>12,13</sup> have shown that there are in fact relevant differences in the outcomes of various antipsychotic treatments. In these reviews, Leucht et al suggest that some second-generation antipsychotics may be more efficacious than others, but that in tailoring drug treatment to the individual patient, efficacy superiorities must be weighed against large differences in treatment-emergent adverse events and cost. How these differences translate into routine clinical practice is not well understood.

The European Schizophrenia Outpatient Health Outcomes (SOHO) study is a large, 3-year, prospective, observational study of the outcomes of antipsychotic treatment for schizophrenia in the outpatient setting that provides a valuable base for comparing the effects of antipsychotics in routine clinical practice. To date, the published results of the SOHO study have focused on reporting the 6-month and 3-year outcomes. However, there has not yet been a paper that reports comprehensively the course of treatment outcomes for the first 12 months of the SOHO study. One year is a timeframe usually employed for planning the delivery of health care services and is often used for the development of economic decision-making models. Thus, reporting the 12-month results of SOHO may provide valuable data to help clinicians, administrators, and policy decision makers to make informed decisions in the treatment of patients with schizophrenia in usual care settings. We report here the results at 12 months of the antipsychotic treatment prescriptions started when patients were recruited into the SOHO study. We present data on a wide range of outcomes including response, remission, treatment maintenance, hospitalization, and treatment tolerability.

## Patients and methods

### Study design

The SOHO study was a 3-year, international, prospective, observational, non-interventional study conducted in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK) and recruited 10,972 patients between September 1, 2000 and December 31, 2001. The study was approved in all countries at the site, regional, or national level, depending on the country regulations and participating sites in each of the countries. Patient informed consent followed country regulations. All patients gave at least oral informed consent, and written informed consent was obtained from patients in Denmark, Italy, Portugal, Spain, Ireland, and the UK. The design and baseline findings of the SOHO study and the 6-month results have been reported elsewhere.<sup>14–17</sup>

Patients participating in the study were adults (aged  $\geq 18$  years) who, at the baseline visit, initiated or changed antipsychotic medication for the treatment of schizophrenia in an outpatient, ambulatory, or community setting, irrespective of the reason for medication change. Patients were included regardless of whether the new antipsychotic drug substituted a previous medication or was an addition to existing treatment, and regardless of the reason for the treatment change. Thus, patients in the SOHO study could be prescribed more than one antipsychotic drug at the baseline visit.

Because the SOHO study had a specific focus on olanzapine, the study design included oversampling of patients starting olanzapine and aimed to provide two patient cohorts of approximately equal size, ie, those who initiated therapy with or changed to olanzapine and those who initiated therapy with or changed to a nonolanzapine antipsychotic.

Each participating psychiatrist was asked to enrol approximately 10 patients, with equal numbers in each of the two patient cohorts. No minimum number of patients per psychiatrist was required and the enrolment period was purposely long. Investigators were instructed to make treatment decisions independent of the study and prior to evaluation of eligibility for inclusion based on entry criteria and the structure of enrolment. Effort was made to avoid any interference with clinical practice. A total of 1096 psychiatrists mostly working in public (46.9%) or combined public and private (37.2%) practices participated.

### Data collection

Data collection occurred during routine outpatient visits and was targeted for baseline, 3 and 6 months post-baseline, and every 6 months thereafter. For each data collection target, investigators were allowed to collect data up to one month before or after the target month. Patients who were not seen during the normal course of care within one assessment interval were not excluded from subsequent data collection. The data collected were similar to those collected in routine clinical practice, including patient demographics, medical resource use, functional status, clinical status, medication use, tolerability, patient-reported and physician-reported adherence, sexual functioning, alcohol and substance abuse, and quality of life.

### Data assessment and analysis

Patients were classified into seven treatment cohorts according to the antipsychotic started at baseline, ie, olanzapine, risperidone, quetiapine, amisulpride, clozapine, oral typical antipsychotic, and depot typical antipsychotic, regardless of

whether they were still receiving that medication at any further visit. Patients who started more than one antipsychotic at the baseline visit were not included in the analyses. However, patients could be taking more than one antipsychotic if they maintained treatment with an antipsychotic that they were taking before baseline, or added a new antipsychotic after baseline. A total of 9608 patients were included in the analysis. Of these, the proportion of patients evaluated at 12 months was 84% (4344/5204) for patients who started olanzapine at baseline, 86% (1596/1863) for patients who started risperidone, 83% (627/760) for patients who started quetiapine, 76% (243/319) for patients who started amisulpride, 92% (289/316) for patients who started clozapine, 86% (579/676) for patients who started an oral typical, and 87% (407/470) for patients who started a depot typical.

## Response

Clinical severity at baseline and response to treatment was assessed using a scale based on the Clinical Global Impression (CGI)<sup>18</sup> that evaluated positive, negative, cognitive, depressive, and overall symptoms on the day of assessment. This was validated as the Clinical Global Impression-Severity for Schizophrenia (CGI-SCH).<sup>19</sup> Scores range from 0 (normal, not ill) to 6 (among the most severely ill).

Response was defined as a decrease (improvement) from baseline of two points in CGI-SCH overall (scale 0–6) if the initial value is 4, 5, or 6; or one point if the initial value is 1, 2, or 3, at least once at either 3, 6, or 12 months. Patients with a score of 0 at baseline were excluded from the analysis of response. Patients who stopped taking their baseline medication before responding were classified as nonresponders.

Quality of life was assessed using the EuroQol-5 Dimensions (EQ-5D), a patient self-rated, generic, health-related quality of life instrument.<sup>20</sup> The EQ-5D is composed of two parts, ie, five questions that assess quality of life in different domains (mobility, self-care, usual activities, pain, and anxiety/depression) and a visual analog scale (EQ-5D VAS) where patients self-rate their overall health on a scale of 0–100, with 0 representing the lowest possible health and 100 the best possible health. Social functioning was assessed using single-item questions that asked whether the patient was involved in any social interactions in the previous 4 weeks (socially active), in a relationship with a spouse or partner, or was exhibiting verbal or physical hostile or aggressive behaviors.

## Remission

Remission was defined as a score of 2 (mild severity) or less on a scale of 0–6 on the CGI-SCH overall severity score, the

CGI-SCH positive symptoms score, the CGI-SCH negative symptoms score and the CGI-SCH cognitive symptoms score, and maintained for two consecutive visits.<sup>21</sup>

## Antipsychotic dose

To enable a comparison of the doses between the cohorts, doses for typical antipsychotics were transformed into olanzapine or haloperidol depot equivalents following a recent consensus which included most typical antipsychotics.<sup>22</sup> However, some medications with equivalences not reported have not been included in the analysis of the dose. Olanzapine 20 mg was used as the reference for the equivalency estimates of oral and long-acting injectable agents. Injectable haloperidol 5 mg was used as the reference for short-acting injectable agents.

## Treatment discontinuation

Treatment discontinuation was defined as stopping the antipsychotic medication started at baseline. If a new treatment was added but the baseline antipsychotic was continued, discontinuation was not considered to have occurred. If a patient did not participate in a visit before switching, he/she was censored (not discontinued) at this visit. The time to discontinuation of treatment was expressed in months, from baseline to the first visit at which the patient discontinued. If a patient discontinued the treatment between two visits, the change was imputed at the mid-point. Survival curves for time to discontinuation over 12 months were constructed using unadjusted Kaplan-Meier estimates. A sensitivity analysis was conducted in which patients not participating in a visit were considered to have discontinued (not censored).

Cox regression models were used to compare the time to medication discontinuation between treatment groups. Since differences among the medication groups could exist at baseline (“selection bias”), the models included the characteristics of the patients at the baseline assessment to address variations that could have affected treatment group differences. Only those variables that remained after performing a stepwise model reduction were kept.

Treatment group comparisons in the changes in CGI-SCH scale scores from baseline over time were made using a mixed model (SAS version 9.0) including the same fixed covariates as for the time to discontinuation, plus baseline CGI-SCH score and time. Time was classified into months (3, 6, and 12 months). The correlation of repeated measures within each patient was modeled with the use of a random intercept and an unstructured covariance matrix. Treatment group comparisons for response at any time during follow-up

were conducted using a logistic regression analysis taking into account baseline covariates.

## Adverse events

Tolerability data included extrapyramidal symptoms (dystonia, akathisia, parkinsonism), tardive dyskinesia, prolactin-related sexual dysfunction (loss of libido/impotence, and presence of amenorrhea/galactorrhea/gynecomastia), and weight and body mass index change by antipsychotic treatment cohort at baseline and at each visit thereafter. Extrapyramidal symptoms and tardive dyskinesia were assessed using a four-point scale (1 = not present; 2 = present but does not significantly interfere with patient's functioning or health-related quality of life; 3 = present and significantly interferes with patient's functioning or health-related quality of life; 4 = present and outweighs therapeutic effect) and counted as present (rating of 2, 3, or 4) or not present (rating of 1). Body weight was recorded by the clinician at each visit without any standardized procedure (ie, no instructions were given on how to measure weight). The appearance of adverse events for those patients not presenting such events at baseline was assessed by medication cohort. A logistic regression model adjusting for baseline differences was used to test for statistical differences between medication cohorts.

## Hospitalization

Differences in frequency of psychiatric hospitalization were described for each of the medication cohorts in the 12 months following baseline.

## Results

A total of 9608 patients were included in the baseline analysis, and 8085 (84.1%) were available for analysis at 12 months. Table 1 shows that approximately half of the patients in the study started olanzapine at baseline (5204/9608, 54%), which is a direct consequence of the study design. The sociodemographic and clinical characteristics of the different cohorts at baseline were similar, except for a few differences (Table 1). Patients in the clozapine cohort tended to be younger and have more severe illness (as indicated by higher mean CGI-SCH ratings) than the other cohorts. Baseline functional status was comparable across the treatment cohorts, except for patients in the clozapine cohort, who tended to have lower social functioning.

## Medication use

Most patients were prescribed treatment with only one antipsychotic after the baseline visit (range 71%–85% across

**Table 1** Demographic and clinical characteristics at baseline assessment by treatment cohort

Characteristic <sup>a</sup>	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral typical	Depot typical
Number (%)	5,204 (54)	1,863 (19)	760 (8)	319 (3)	316 (3)	676 (7)	470 (5)
Gender (% female)	41	42	47	44	36	49	41
Age, years	40 (13)	40 (13)	41 (13)	39 (13)	37 (10)	41 (13)	42 (12)
Age at first treatment contact for schizophrenia, years	29 (11)	29 (10)	28 (10)	30 (12)	24 (7)	29 (10)	29 (10)
CGI <sup>b</sup> overall severity	3.42 (1.00)	3.36 (0.97)	3.36 (1.02)	3.33 (0.99)	3.76 (1.00)	3.35 (1.09)	3.41 (0.99)
CGI-SCH positive symptoms	2.76 (1.44)	2.80 (1.39)	2.62 (1.50)	2.54 (1.40)	3.39 (1.41)	2.93 (1.47)	3.05 (1.41)
CGI-SCH negative symptoms	3.08 (1.28)	3.00 (1.24)	3.10 (1.29)	3.17 (1.29)	3.13 (1.31)	2.82 (1.36)	2.97 (1.25)
CGI-SCH depressive symptoms	2.48 (1.33)	2.37 (1.31)	2.50 (1.31)	2.44 (1.40)	2.48 (1.32)	2.37 (1.30)	2.21 (1.33)
CGI-SCH cognitive symptoms	2.75 (1.33)	2.71 (1.29)	2.76 (1.30)	2.87 (1.34)	2.91 (1.32)	2.74 (1.32)	2.73 (1.30)
EQ-5D VAS <sup>c</sup> rating	45.71 (21.11)	46.91 (20.50)	47.59 (21.04)	45.57 (23.06)	41.98 (21.67)	47.43 (22.04)	48.76 (21.15)
Socially active <sup>d</sup> (%)	3,414 (66)	1,276 (70)	505 (67)	222 (71)	203 (65)	466 (70)	310 (66)
Paid employment (%)	1075 (21)	372 (20)	120 (16)	73 (23)	48 (15)	127 (19)	68 (15)

**Notes:** <sup>a</sup>Values are means (SD) unless otherwise indicated; <sup>b</sup>CGI-SCH: scale 0 (normal, not ill at all) to 6 (among the most severely ill); <sup>c</sup>VAS: 0 (worst) to 100 (best); <sup>d</sup>any social contact in the 4 weeks prior to assessment; percentages may not add up to 100 due to rounding.

**Abbreviations:** SD, standard deviation; CGI-SCH, Clinical Global Impression-Schizophrenia; EQ-5D, EuroQol-5 Dimensions; VAS, visual analog scale.

cohorts, Table 2). In general, the mean doses of antipsychotic medication prescribed at baseline remained stable at 12 months, although there was noticeable dose titration with quetiapine and clozapine (Table 2).

## Response

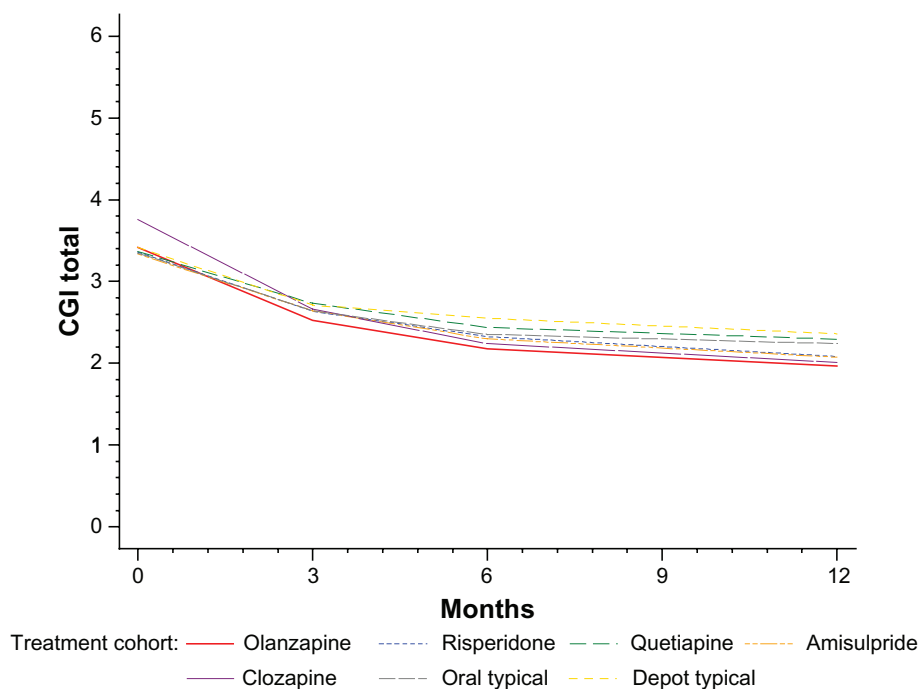
Figure 1 shows the improvement in CGI-SCH overall severity scores from baseline to 12 months, by treatment cohort. Although most improvement occurred in the first 3 months after baseline, there was continued improvement during 3 to 12 months in all cohorts. Clinical and social outcomes at 12 months are summarized in Table 3. The percentage of patients responding to treatment based on CGI-SCH overall symptom severity ranged from 64% in the olanzapine and clozapine cohorts to 45% in the amisulpride cohort. Patient health-related quality of life (EQ-5D VAS) increased from about 45 at baseline to around 60 at the 12-month visit. Some differences were present among cohorts. Response rates based on CGI-SCH subscales were generally greatest with olanzapine; these ranged from 52% in the quetiapine cohort to 67% in the olanzapine cohort for positive symptoms, from 42% in the depot typical cohort to 61% in the olanzapine cohort for negative symptoms, 40% in the depot typical cohort to 61% in the olanzapine cohort for cognitive symptoms, and 48% in the oral typical cohort to 67% in the olanzapine cohort for depressive symptoms.

The multivariate models that have been fitted allow the comparison between the treatment cohorts adjusting for the baseline differences that originated in the observational nature of SOHO. Table 4 shows results of the multivariate analysis for each outcome in each treatment cohort relative to the olanzapine cohort and adjusted for baseline differences between the cohorts. The change in CGI-SCH overall from baseline showed that symptom improvement for patients in the risperidone, quetiapine, and oral and depot typical antipsychotic cohorts was significantly lower than in the olanzapine cohort. Compared with olanzapine, patients in all cohorts, except clozapine, had a significantly lower likelihood of achieving a response in CGI-SCH overall. Patients in all cohorts except the clozapine cohort had a lower increase in EQ-5D VAS at 12 months compared with olanzapine. For CGI-SCH positive symptoms, patients in the risperidone, quetiapine, amisulpride, and oral typical and depot typical antipsychotic cohorts had a significantly lower response than those in the olanzapine cohort (Table 4). Compared with olanzapine, Table 4 also shows that patients in all cohorts except clozapine were less likely to demonstrate a response in CGI-depressive symptoms than those in the olanzapine cohort.

**Table 2** Pharmacological treatment patterns by treatment cohort

	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral typical	Depot typical
Treated with only one antipsychotic after the baseline visit, %	82	85	76	82	84	71	76
Patients on monotherapy							
Mean (SD) dose at baseline, mg	10.7 (5.2)	4.4 (2.4)	251.7 (172.6)	360.3 (244.9)	156.2 (125.9)	19.8 (65.3)	50.1 (53.1)
Mean (SD) dose at 12 months, mg	12.0 (5.9)	4.9 (2.7)	388.4 (214.7)	415.2 (261.8)	244.8 (133.0)	33.6 (150.5)	52.5 (54.7)
Patients on combination therapy							
Mean (SD) dose at baseline, mg	10.4 (5.3)	3.9 (2.3)	222.4 (190.9)	296.5 (180.0)	116.8 (114.0)	43.9 (109.9)	48.9 (47.6)
Mean (SD) dose at 12 months, mg	13.9 (6.5)	5.6 (3.4)	445.7 (263.6)	522.5 (253.7)	267.6 (186.8)	25.9 (50.9)	63.4 (54.8)

**Notes:** All doses are converted into chlorpromazine equivalent doses; percentages may not add up to 100 due to rounding.  
**Abbreviation:** SD, standard deviation.



**Figure 1** CGI-SCH scores over 12 months, by treatment cohort.

**Abbreviations:** CGI, Clinical Global Impression; CGI-SCH, Clinical Global Impression-Severity for Schizophrenia.

## Social outcomes

The percentage of patients who were socially active ranged from 52% in the quetiapine cohort to 70% in the olanzapine cohort (Table 3). The multivariate models which adjusted for baseline covariates showed that patients in the olanzapine cohort were more likely to be socially active (Table 4).

## Remission

Of the 9079 patients analyzed for remission, a total of 3189 (35.1%) achieved remission over the 12-month period. Remission rate was highest in the clozapine cohort and lowest in the quetiapine cohort; remission was achieved by 1913 (39.1%) olanzapine-treated patients, 594 (33.5%) risperidone-treated patients, 174 (24.4%) quetiapine-treated patients, 74 (25.2%) amisulpride-treated patients, 122 (40.0%) clozapine-treated patients, 194 (29.8%) oral typical-treated patients, and 118 (26.1%) depot typical-treated patients.

The regression analysis demonstrated that the likelihood of achieving remission over the 12-month period was significantly more likely with olanzapine than with any of the other antipsychotics except for clozapine. Compared with olanzapine, the odds ratio of achieving remission was 0.569 (95% CI 0.422–0.768,  $P = 0.0002$ ) for amisulpride, 1.358 (95% CI 1.045–1.765,  $P = 0.0219$ ) for clozapine, 0.555 (95% CI 0.437–0.704,  $P < 0.0001$ ) for depot typical, 0.581 (95% CI 0.476–0.709,  $P < 0.0001$ ) for oral typical, 0.454 (95% CI

0.372–0.554,  $P < 0.0001$ ) for quetiapine, and 0.712 (95% CI 0.626–0.810,  $P < 0.0001$ ) for risperidone.

## Treatment discontinuation

Time to discontinuation by treatment cohort is shown in Figure 2. The risk of treatment discontinuation at 12 months was lowest and similar for olanzapine and clozapine, slightly higher for risperidone and depot typicals, and highest for quetiapine, amisulpride, and oral typicals. The sensitivity analysis (in which patients not participating in a visit were considered to have discontinued rather than just censored) is shown in Figure 3; the rank order of risk of discontinuation with different cohorts remained the same in the sensitivity analysis.

The results of the Cox's proportional hazards model that analyzed differences in discontinuation rate showed that discontinuation was lowest for olanzapine and clozapine and that all medications except for clozapine had a higher discontinuation rate than olanzapine. Hazards ratios were 1.39 for risperidone (95% CI 1.22–1.59), 2.34 for quetiapine (95% CI 2.00–2.72), 2.39 for amisulpride (95% CI 1.92–2.98), 2.31 for oral typical (95% CI 1.97–2.71), and 1.48 for depot typical (95% CI 1.19–1.84).

## Adverse events

Adverse events at 12 months are summarized in Table 5. The occurrence of extrapyramidal symptoms at 12 months

**Table 3** Clinical and social outcomes at 12 months

Outcomes <sup>a</sup>	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral typical	Depot typical
CGI-SCH overall at 12 months, mean (SD)	2.0 (1.1)	2.1 (1.1)	2.3 (1.2)	2.1 (1.2)	2.0 (1.2)	2.2 (1.2)	2.4 (1.2)
Response <sup>b</sup> at any time in CGI-SCH overall symptoms	64	55	46	45	64	47	48
EQ-5D VAS rating, mean (SD)	65.9 (19.3)	63.5 (18.4)	63.1 (19.6)	59.9 (21.3)	63.4 (19.9)	60.9 (20.3)	63.1 (18.5)
Response <sup>b</sup> in CGI-SCH positive symptoms	67	62	52	53	65	55	53
Response <sup>b</sup> in CGI-SCH negative symptoms	61	52	47	44	60	44	42
Response <sup>b</sup> in CGI-SCH cognitive symptoms	61	54	47	43	59	43	40
Response <sup>b</sup> in CGI-SCH depressive symptoms	67	58	55	55	66	48	50
Symptom remission	39	34	24	25	40	30	26
Socially active	70	66	52	53	67	54	60
Paid employment, number (%)	20	17	11	15	15	13	11
Any hospitalization during follow-up	13	14	20	24	16	16	18

**Notes:** <sup>a</sup>Outcomes values are % unless otherwise indicated; <sup>b</sup>response defined as a decrease of 2 points from a baseline of 4–6 points or a decrease of 1 point from a baseline of 1–3 points.

**Abbreviations:** CGI-SCH, Clinical Global Impression-Schizophrenia; SD, standard deviation; EQ-5D, EuroQol-5 Dimensions; VAS, visual analog scale.

**Table 4** Social and clinical outcomes at 12 months: odds ratios from multivariate analysis comparing olanzapine with the other treatment cohorts

Outcomes <sup>a</sup>	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral typical	Depot typical
Change in CGI-overall from baseline, difference (SE)	0	0.16 (0.03) <sup>c</sup>	0.28 (0.04) <sup>c</sup>	0.16 (0.06)	-0.06 (0.05)	0.26 (0.04) <sup>c</sup>	0.26 (0.05) <sup>c</sup>
Response in CGI-overall	1	0.68	0.47	0.51	1.00	0.48	0.55
Difference in EQ-5D VAS from baseline (95% CI)	0	0.60; 0.76 <sup>c</sup>	0.40; 0.56 <sup>c</sup>	0.39; 0.65 <sup>c</sup>	0.78; 1.28	0.40; 0.57 <sup>c</sup>	0.45; 0.68 <sup>c</sup>
Response in CGI-SCH positive symptoms	1	-2.66	-2.84	-4.51	0.13	-4.42	-4.11
Response in CGI-SCH negative symptoms	1	-3.52; -1.79 <sup>c</sup>	-4.14; -1.55 <sup>c</sup>	-6.52; -2.50 <sup>c</sup>	-1.67; 1.93	-5.76; -3.08 <sup>c</sup>	-5.63; -2.59 <sup>c</sup>
Response in CGI-SCH cognitive symptoms	1	0.81 (0.71; 0.92) <sup>b</sup>	0.53 (0.44; 0.63) <sup>c</sup>	0.64 (0.49; 0.83) <sup>b</sup>	0.85 (0.66; 1.11)	0.59 (0.50; 0.71) <sup>c</sup>	0.55 (0.45; 0.68) <sup>c</sup>
Symptom remission	1	0.75 (0.66; 0.84) <sup>c</sup>	0.55 (0.46; 0.65) <sup>c</sup>	0.51 (0.39; 0.66) <sup>c</sup>	0.89 (0.69; 1.14)	0.46 (0.40; 0.57) <sup>c</sup>	0.49 (0.40; 0.60) <sup>c</sup>
Socially active	1	0.71 (0.63; 0.81) <sup>c</sup>	0.45 (0.37; 0.55) <sup>c</sup>	0.57 (0.42; 0.77) <sup>b</sup>	0.90 (0.70; 1.17)	0.46 (0.38; 0.55) <sup>c</sup>	0.45 (0.36; 0.56) <sup>c</sup>
Response in CGI-SCH depressive symptoms	1	0.73 (0.53; 0.99)	0.50 (0.32; 0.78)	0.57 (0.29; 1.13)	0.69 (0.37; 1.28)	0.58 (0.48; 0.71) <sup>c</sup>	0.56 (0.44; 0.70) <sup>c</sup>
Any hospitalization during follow-up	1	0.67 (0.59; 0.76) <sup>c</sup>	0.62 (0.52; 0.74) <sup>c</sup>	0.56 (0.43; 0.74) <sup>c</sup>	0.95 (0.73; 1.25)	0.46 (0.39; 0.56) <sup>c</sup>	0.54 (0.42; 0.66) <sup>c</sup>
	1	1.18 (0.98; 1.41)	1.77 (1.40; 2.24) <sup>c</sup>	1.81 (1.30; 2.51) <sup>b</sup>	1.04 (0.72; 1.48)	1.54 (1.20; 1.98) <sup>b</sup>	1.52 (1.15; 2.00)

**Notes:** <sup>a</sup>Values are odds ratios (95% CI) unless otherwise indicated. Odds ratio > 1 indicates a lower response compared with olanzapine cohort; adjusted difference > 0 indicates better outcome compared with the olanzapine cohort; <sup>b</sup>p < 0.001; <sup>c</sup>p < 0.0001.

**Abbreviations:** CGI, clinical global impression; SE, standard error; EQ-5D, EuroQol-5 Dimensions; VAS, visual analog scale; CI, confidence intervals.

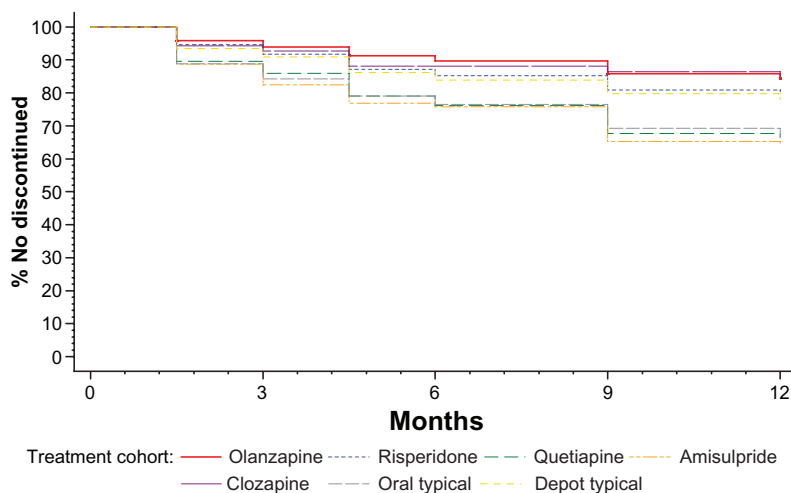


Figure 2 Time to discontinuation over 12 months, by treatment cohort.

was least in the olanzapine cohort (8%) and greatest in the depot typical cohort (31%); compared with olanzapine, the likelihood of experiencing extrapyramidal symptoms was increased with all antipsychotics except clozapine and quetiapine. Loss of libido was lowest in the clozapine cohort (17%) and highest in the amisulpride cohort (30%); compared with olanzapine, the likelihood of experiencing loss of libido was increased in patients taking risperidone or typical antipsychotics. Impotence/sexual dysfunction were lowest in the quetiapine cohort (12%) and highest in the amisulpride and oral typical cohorts (22%); compared with olanzapine, impotence/sexual dysfunction was higher with all antipsychotics except for quetiapine. The frequency of gynecomastia and galactorrhea after 12 months of treatment was low in all cohorts; at 12 months gynecomastia ranged from 2% to 5%, and galactorrhea ranged from 1% to 4%. Compared with

olanzapine, the likelihood of experiencing amenorrhea was increased in the risperidone, amisulpride, and depot typical antipsychotic cohorts. Mean weight increased during the 12 months of treatment in all treatment cohorts; increases in mean weight from baseline to 12 months ranged from 3.2 kg in the olanzapine cohort to 0.6 kg in the quetiapine cohort. Compared with olanzapine, patients in other cohorts were significantly less likely to experience weight gain, except for clozapine. Clinically significant weight gain ( $\geq 7\%$  body weight) from baseline to 12 months occurred in 1379 (28.1%) olanzapine-treated patients, 323 (18.3%) risperidone-treated patients, 109 (15.4%) quetiapine-treated patients, 56 (19.0%) amisulpride-treated patients, 60 (19.6%) clozapine-treated patients, 121 (18.7%) oral typical-treated patients, and 89 (19.7%) depot typical-treated patients. The likelihood of experiencing clinically significant weight gain was higher in

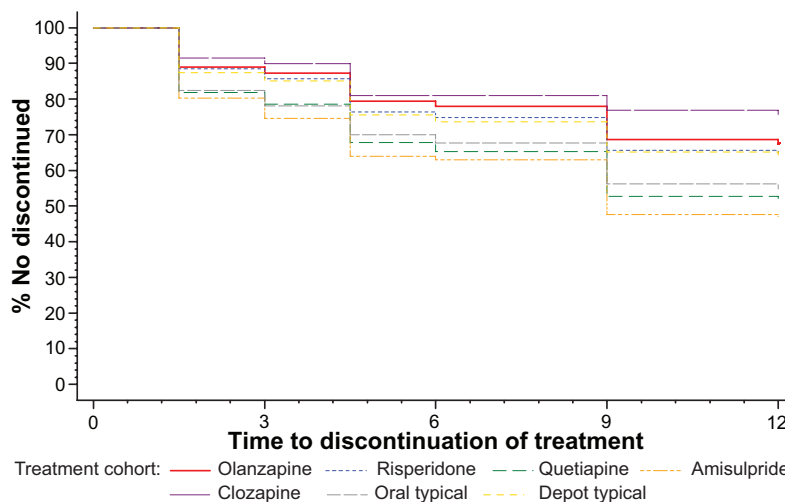


Figure 3 Time to discontinuation over 12 months, by treatment cohort: sensitivity analysis (patients not participating in a visit were considered to have discontinued).



Table 5 Appearance of adverse events during the 12 months of follow-up

Adverse event	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral typical	Depot typical
<b>EPS</b>							
Patients experiencing new event, %	8	20	11	18	12	21	31
Odds ratio	1	2.27	1.20	1.51	0.95	2.39	4.12
95% CI	–	1.99; 2.59 <sup>c</sup>	0.98; 1.47	1.12; 2.04 <sup>a</sup>	0.69; 1.29	1.97; 2.88 <sup>c</sup>	3.33; 5.11 <sup>c</sup>
<b>TD</b>							
Patients experiencing new event, %	1.9	3.5	2.5	3.5	3.3	6.0	6.1
Odds ratio	1	1.29	1.08	1.42	1.22	1.69	1.79
95% CI	–	1.03; 1.63 <sup>a</sup>	0.78; 1.51	0.92; 2.21	0.75; 1.99	1.25; 2.29 <sup>b</sup>	1.29; 2.50 <sup>b</sup>
<b>Loss of libido</b>							
Patients experiencing new event, %	23	29	21	30	17	29	28
Odds ratio	1	1.33	1.13	1.17	1.17	1.55	1.36
95% CI	–	1.18; 1.51 <sup>c</sup>	0.95; 1.35	0.90; 1.53	0.91; 1.52	1.29; 1.86 <sup>c</sup>	1.10; 1.68 <sup>a</sup>
<b>Impotence/sexual dysfunction</b>							
Patients experiencing new event, %	16	20	12	22	18	22	19
Odds ratio	1	1.44	1.06	1.43	1.34	1.49	1.35
95% CI	–	1.27; 1.64 <sup>c</sup>	0.88; 1.28	1.10; 1.88 <sup>a</sup>	1.02; 1.76 <sup>c</sup>	1.23; 1.79 <sup>c</sup>	1.08; 1.68 <sup>a</sup>
<b>Gynecomastia</b>							
Patients experiencing new event, %	2	2	2	5	2	3	3
Odds ratio	1	1.08	1.47	0.98	1.62	1.30	1.20
95% CI	–	0.78; 1.49	0.98; 2.21	0.53; 1.81	0.93; 2.83	0.84; 2.02	0.72; 1.98
<b>Galactorrhea</b>							
Patients experiencing new event, %	1	2	1	4	1	2	2
Odds ratio	1	1.77	1.16	1.89	0.82	1.35	1.51
95% CI	–	1.18; 2.65 <sup>c</sup>	0.60; 2.24	0.87; 4.14	0.25; 2.67	0.72; 2.54	0.74; 3.09
<b>Amenorrhea</b>							
Patients experiencing new event, %	4	7	5	10	4	5	6
female patients							
Odds ratio	1	2.01	1.18	2.23	1.30	1.11	1.71
95% CI	–	1.64; 2.46 <sup>c</sup>	0.88; 1.59	1.47; 3.38 <sup>a</sup>	0.83; 2.06	0.82; 1.51	1.21; 2.41 <sup>a</sup>
<b>Weight</b>							
Change to 12 months (kg) mean (SD)	3.2 (8.5)	1.8 (6.6)	0.6 (6.1)	1.1 (9.7)	2.1 (7.9)	1.4 (7.5)	1.5 (8.0)
Adjusted differences in weight change	0	–0.83	–1.14	–1.38	–0.42	–1.24	–1.18
95% CI	–	–1.22; –0.43 <sup>c</sup>	–1.73; –0.56 <sup>a</sup>	–2.29; –0.47	–1.24; 0.39	–1.85; –0.63 <sup>c</sup>	–1.87; –0.49 <sup>a</sup>
<b>Clinically significant weight gain</b>							
Patients experiencing event, %	28	18	15	19	20	19	20
Adjusted odds ratio	1	0.56	0.46	0.71	0.60	0.57	0.67
95% CI	–	(0.48–0.65) <sup>c</sup>	0.36; 0.58 <sup>c</sup>	0.51; 0.99 <sup>a</sup>	0.44; 0.82 <sup>a</sup>	0.46; 0.72 <sup>c</sup>	0.52; 0.87

**Notes:** Percentages may not add up to 100 due to rounding. <sup>a</sup>*p* < 0.05; <sup>b</sup>*p* < 0.001; <sup>c</sup>*p* < 0.0001.

**Abbreviations:** EPS, extrapyramidal symptoms; CI, confidence interval; TD, tardive dyskinesia; SD, standard deviation.

the olanzapine cohort than in all other antipsychotic cohorts. At 12 months, the increase in body mass index category across the cohorts ranged from 13% (with quetiapine and depot typicals) to 21% (with olanzapine).

## Hospitalization

Hospitalization in the different medication cohorts during the 12 months following baseline ranged from 13%–24%; hospitalization occurred in 607 (13%) olanzapine-treated patients, and in 240 (14%) risperidone, 137 (20%) quetiapine, 70 (24%) amisulpride, 49 (16%) clozapine, 105 (16%) oral typical, and 79 (18%) depot typical-treated patients. Compared with olanzapine, the odds ratios for hospitalization were higher in the other cohorts except clozapine and risperidone.

## Discussion

The SOHO study is the largest prospective observational investigation of the long-term use and outcomes associated with antipsychotic drugs in schizophrenia to have been conducted to date. This analysis of 12-month SOHO data found that the cohorts of patients treated with olanzapine and clozapine tended to have a better clinical course than patients treated with other atypical or typical antipsychotics. Patients receiving olanzapine or clozapine had a higher response rate when using CGI-SCH overall symptom severity and when assessing specific symptom domains, ie, positive, negative, cognitive, and depressive symptoms. In addition, the differences in clinical outcomes were associated with greater improvements in patient health-related quality of life as well as in some aspects of social functioning. Treatment discontinuation, which is considered the best method to assess effectiveness of antipsychotics,<sup>23</sup> was also lower. With regard to remission, regression analysis demonstrated that the likelihood of achieving remission over the 12-month period was significantly higher with olanzapine and clozapine than with the other studied antipsychotics.

Current findings of better outcomes with olanzapine and clozapine compared with other antipsychotics are consistent with prior studies comparing different antipsychotic drugs, such as the CATIE study,<sup>23</sup> the meta-analyses of randomized controlled trials comparing the effectiveness of antipsychotics conducted by Leucht et al,<sup>12,13</sup> and the findings of the large-scale observational study conducted by Tiihonen et al.<sup>24</sup> Therefore, these 12-month findings from the SOHO study add to the body of evidence suggesting that there are differences in the outcomes of treatment with various antipsychotics.

In the present study, improvements in clinical outcomes at 12 months were translated into improvements in patient health-related quality of life and social functioning. Quality of life was assessed using the EQ-5D, a generic instrument that has been validated in patients with schizophrenia from the 10 countries included in the SOHO study,<sup>25</sup> and which is sensitive enough to pick up differences between patients with varying severities of illness.<sup>26</sup> Improvement in quality of life was slightly greater for patients in the olanzapine cohort compared with the risperidone, amisulpride, quetiapine, and typical and depot antipsychotic cohorts. Improvements in quality of life have been noted previously with atypical antipsychotics and are greater than those seen with typical antipsychotics.<sup>27,28</sup> We also found evidence of some improvement in social functioning. There were some differences between treatment cohorts in these functional outcomes, and patients treated with typical antipsychotics were found to be less socially active than those treated with olanzapine. Similar findings have been reported previously in a comparison between olanzapine and haloperidol.<sup>29</sup>

Antipsychotic dose can be of great importance in the interpretation of effectiveness and the prevalence and severity of treatment-emergent adverse events. In general, the dosage range is not only related to optimal efficacy, but can also be related to the prevalence of adverse events. The antipsychotic doses used in the SOHO study are consistent with those from previous long-term and mid-term studies, clinical experience, and pharmacological guidelines for schizophrenia. The mean dose of olanzapine used in SOHO (12.0 mg/day) is similar to that used by other investigators<sup>30</sup> and appears to be optimal in the treatment of outpatients with schizophrenia.<sup>31</sup> The mean dosage used in the risperidone cohort (5.0 mg/day) was also similar to the modal dose (4.8 mg/day) used in a study by Conley and Mahmoud.<sup>32</sup> The dose for amisulpride (mean 415 mg/day) is at the lower end of the recommended range (400–800 mg/day),<sup>33</sup> and the dose for quetiapine (mean 388 mg/day) is slightly below the recommended dose (400 mg/day);<sup>34</sup> in both medications there was an upward dose titration during the course of the study. Although used in clinical practice in a wide range, the mean clozapine dose in the SOHO study (245 mg/day) is lower than that recommended by the manufacturer.<sup>35</sup>

Antipsychotic discontinuation for any cause is considered a powerful indicator of medication effectiveness in schizophrenia<sup>23</sup> because it reflects the medication's efficacy, safety, and tolerability from both the patient and clinician perspectives. In the CATIE study, olanzapine was the antipsychotic with the lowest rate of all-cause

medication discontinuation.<sup>23</sup> The risk of treatment discontinuation at 12 months in SOHO was also the lowest and similar for olanzapine and clozapine. However, rates of 12-month antipsychotic treatment maintenance reported here were higher than in CATIE<sup>23</sup> which might be related to the double-blind design of the CATIE study. Other observational studies also support the higher effectiveness of olanzapine compared with other antipsychotics.<sup>24</sup>

With regard to treatment-emergent adverse events, the olanzapine, quetiapine, and clozapine cohorts had, at 12 months, the lowest proportion of patients with extrapyramidal symptoms, while the risperidone and oral and depot typical antipsychotic cohorts had the highest proportions. In a meta-analysis of randomized clinical trials, patients treated with olanzapine, quetiapine, risperidone, and sertindole were found to use less antiparkinsonian medication than haloperidol-treated patients.<sup>36</sup> Moreover, the higher incidence of extrapyramidal symptoms in the risperidone cohort is also consistent with previous reports showing that risperidone-induced extrapyramidal symptoms are dose-dependent.<sup>37</sup>

Patients treated with olanzapine, clozapine, and quetiapine were significantly less likely to have sexual dysfunction after 12 months of treatment than those in the other treatment cohorts; these adverse events were much more likely to occur in patients treated with oral typical or depot typical antipsychotics, risperidone, and amisulpride. These findings are in line with other studies reporting that olanzapine is associated with less sexual dysfunction than risperidone or typical antipsychotics,<sup>38,39</sup> and that quetiapine is associated with a low incidence of sexual dysfunction.<sup>39</sup>

The mechanisms underlying sexual dysfunction in antipsychotic-treated patients are poorly understood but may be related to increased prolactin levels, and prolactin levels may be 10 times higher than normal in some patients receiving antipsychotics.<sup>40</sup> Elevated prolactin levels are common during treatment with amisulpride and risperidone, whereas olanzapine-, quetiapine-, and clozapine-treated patients experience modest elevations on prolactin levels during chronic administration.<sup>41,42</sup> Treatment-emergent sexual dysfunction is distressing for patients and may result in nonadherence with medication, which in turn can result in treatment failure.

Rates of obesity in schizophrenia are a cause for concern because they are higher than in the general population.<sup>43</sup> Weight gain, as an adverse event of treatment with antipsychotic medications, is an important problem because it may contribute to the increased risk for obesity-associated problems,<sup>44,45</sup> and may also affect adherence to medication.<sup>46</sup> A meta-analysis of 81 studies revealed that among the

antipsychotic agents examined, clozapine and olanzapine were associated with the greatest increase in weight at 10 weeks.<sup>47</sup>

The results from the present study confirm previous findings that many antipsychotics, both typical and atypical agents, are associated with weight gain. Consistently with the meta-analysis reported above, the increases in weight were significantly greater in the olanzapine cohort than in the other treatment cohorts, except clozapine.

The mechanisms underlying antipsychotic treatment-emergent weight gain are unclear, but may be caused by a number of factors, including effects on neurotransmission (such as dopamine, serotonin, or histamine), interactions with hormones, and several environmental factors.<sup>45,48</sup> Some patients may have a genetic predisposition to antipsychotic treatment-emergent weight gain.<sup>48</sup>

There is little information on how the results from one region of the world generalize to other areas. There is some evidence that the course of schizophrenia varies among regions of the world.<sup>49</sup> However, it is not clear if medication effects or differences also vary in the different countries. Luckily, studies with very similar or exact designs as the SOHO study have been conducted in different continents (eg, Intercontinental-SOHO)<sup>50</sup> and in Japan.<sup>51</sup> The results of those studies are largely consistent. For example, the baseline characteristics of the patients initiated on olanzapine in the SOHO study appear similar to those of the outpatients in the Japanese study in terms of average age ( $40.0 \pm 13.4$  and  $38.3 \pm 13.9$  years, respectively), gender (41.1% and 49.6% female), or CGI-SCH global severity in the moderately ill range ( $3.4 \pm 1.0$  and  $3.0 \pm 1.0$ ). In addition, treatment outcomes for outpatients on the core outcome domains in the Japanese study were similar to those observed in the European SOHO study. For example, the percent of patients remaining on treatment for 1 year was 63.8% for the outpatients in the Japanese study and only slightly higher in this study; functional improvement on the EQ-5D VAS score from baseline to endpoint was similar for SOHO participants (change from 45.7 to 65.2) and the outpatient participants in the Japanese study (change from 45.3 to 65.3); percent of participants working for pay at endpoint was almost identical for participants in SOHO (20.3%) and the outpatients in the Japanese study (20.5%).<sup>52</sup>

## Limitations

SOHO is an observational study and several aspects of the study design are worthy of discussion. Firstly, approximately half of the patients started therapy with olanzapine due to

the study design (oversampling of the olanzapine cohort). This does not change the observational nature of the study nor does it influence the interpretation of the results because the statistical analysis adjusts for the different sizes of the treatment cohorts. Secondly, assignment to treatment cohort was not random, in that psychiatrists decided which drug to initiate in which patients and at what dose. Importantly, this led to the presence of baseline differences between cohorts. The multivariate analysis employed adjusted for all observed baseline differences between cohorts. Previous research has found that when observational studies have appropriate designs and analysis strategies, comparisons of the findings of randomized controlled trials and observational studies reveal no major differences in the effects of treatments.<sup>53,54</sup> An important limitation of the SOHO study is that the assessment by participating psychiatrists was not blind and this could lead to outcome bias in favor of the olanzapine cohort, especially given that the company that produces olanzapine is supporting the study. However, as reported previously, differences between treatment cohorts in physician-rated clinical status (CGI) are accompanied by differences in health-related quality of life, which is a patient self-reported measure and thus observer bias does not seem to have a relevant effect in the SOHO study.<sup>54</sup> Finally, in the search for simplicity of assessment, several dimensions of social functioning and the presence of adverse events were measured using single-item questions and may, therefore, have lower sensitivity and precision than specific instruments used to measure adverse events, such as the Simpson-Angus Scale for extrapyramidal symptoms<sup>55</sup> or the Abnormal Involuntary Movement Scale.<sup>18</sup>

The SOHO study has several strengths worth mentioning. Due to its large size, powerful statistical techniques can be used to control for confounding factors. There was a high retention rate in the study, much higher than that seen in randomized controlled trials, where high dropout rates may limit the drawing of firm conclusions. This high retention rate may partly be due to the treatment flexibility allowed, such that physicians could change a patient's medication and/or dosage as deemed necessary while patients continued to be evaluated. Additionally, there were no protocol-defined clinical reasons to discontinue patients from SOHO. These methodological differences may help to explain why we find differential clinical responses between antipsychotic medications that are not present in randomized clinical trials. Despite the treatment flexibility allowed, we found that at 12 months, the majority of patients were still on the same medication they had started at baseline. Further-

more, we used several outcome measures to represent fully the characteristics of the course of schizophrenia, including response short-term treatment outcomes and remission for long-term treatment outcomes.

## Conclusion

This analysis of 12-month data from the large observational SOHO study found that outpatients with schizophrenia who required initiation or a change in their antipsychotic for clinical reasons showed a marked improvement in symptoms, that translated into improvements in their health-related quality of life and in some dimensions of social functioning. The cohorts of patients treated with olanzapine and clozapine tended to have a better clinical course than patients treated with other atypical or typical antipsychotics.

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