Long-Term Antipsychotic Monotherapy for Schizophrenia: Disease Burden and Comparative Outcomes for Patients Treated With Olanzapine, Quetiapine, Risperidone, or Haloperidol Monotherapy in a Pan-Continental Observational Study

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Objective: Noninterventional, naturalistic studies facilitate examination of current clinical practices and provide an understanding of the impact of the biopsychosocial aspects of schizophrenia. This article describes disease burden and patient outcomes, with an emphasis on the comparative effectiveness and tolerability of antipsychotic monotherapy.

Method: Outpatients initiating or changing antipsychotic therapy for DSM-IV– or ICD-10–defined schizophrenia (N = 7658) were allocated to olanzapine or nonolanzapine cohorts (November 2000 to December 2001). Treatment was at the psychiatrist's discretion, including flexible dosing and use of concomitant therapies and medications, with assessments at 0, 3, 6, 12, 18, 24, 30, and 36 months. Longitudinal clinical, pharmacologic, functional, and social data were collected over 36 months across 27 countries.

Results: At entry, 76% of patients were initiated/switched to antipsychotic monotherapy, most commonly with olanzapine (N = 3222), risperidone (N = 1117), quetiapine (N = 189), or haloperidol (N = 257). Patients prescribed olanzapine were more likely to maintain their baseline monotherapy ($p < .001$) and did so for a longer period ($p < .001$) compared with other antipsychotics. Median time to discontinuation (in months) was as follows: olanzapine 30.0, risperidone 23.1, quetiapine 13.9, haloperidol 12.5. Olanzapine-treated patients were also more likely to respond, and did so more rapidly than patients on other monotherapies ($p < .001$). Response data were also favorable for risperidone; median time to response (in months) was as follows: olanzapine 5.2, risperidone 6.3, quetiapine 11.3, haloperidol 11.7. Treatment-emergent adverse events varied: olanzapine patients had less favorable odds for significant weight gain ($p < .001$); haloperidol patients, for motor dysfunction ($p \leq .002$).

Conclusion: These naturalistic data from less-studied outpatient communities highlight the variability in clinical and functional outcomes associated with long-term antipsychotic treatment.

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Schizophrenia affects about 1% of the population worldwide,[1] although the prevalence rate is subject to variation.[2] However, as a chronic and disabling mental illness with a variable course, and symptoms including cognitive dysfunction and florid psychoses, the burden of illness and associated costs are disproportionately high.[3] The World Health Organization currently estimates that less than half of the people with schizophrenia receive appropriate care[4]; a relatively recent review of 37 community-based psychiatric epidemiology studies found that, for schizophrenia and nonaffective psychoses, at least one third of patients are untreated.[5] This treatment gap is despite the fact that a range of effective

pharmacologic and psychosocial treatments exist, and it occurs even in resource-rich countries. Moreover, a recent assessment of the cost-effectiveness of schizophrenia treatment in Australia found that, for no extra cost, optimal treatment would alleviate an additional 9% of the disease burden unaffected by current interventions (which avert 13% of the disease burden).[6]

In recent years, the paradigm of treatment success has shifted from the control of symptoms to the effective management and reintegration of patients into the community. Accordingly, the need for appropriate assessment of treatments outside of the clinical trial setting has risen. Antipsychotics are the mainstay of schizophrenia treatment, with atypical antipsychotics recommended as a first-line treatment in most large guidelines, including those of the American Psychiatric Association[7] and the National Institute for Health and Clinical Excellence in the United Kingdom.[8] While the efficacy and tolerability of this diverse group of antipsychotics have been established by randomized controlled trials (RCTs), these are usually short-term studies in restricted patient populations. Indeed, comparison of patients in RCTs with those in actual clinical practice revealed that between 38% and 55% of patients in a psychiatric practice network would not have been eligible for inclusion in an RCT, mainly due to comorbidities and medication regimens.[9]

Effectiveness is a construct that RCTs (or explanatory trials), by their very design, are unable to fully address. Unlike efficacy, which establishes whether a treatment works in ideal conditions, effectiveness measures how well the treatment works in actual clinical practice.[10] Thus, pragmatic trials afford an understanding of the benefit a treatment produces in routine clinical care. Antipsychotics are not curative; they provide effective management of symptoms, but schizophrenia requires flexible long-term management to achieve sustainable improvements and good patient outcomes measured not only by symptom severity, but also by social and occupational dysfunction and quality of life. Adherence to recommended therapy and relapse prevention are among the most important aims of treatment. One to 10 consecutive days without medication within a year have been shown to double a patient's risk of hospitalization, highlighting the importance of medication adherence.[11] Observational studies assess the relevance and credibility of outcomes achieved in clinical trials in actual clinical practice settings. The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study sought to include patients representative of those receiving treatment for schizophrenia in outpatient settings from less-studied communities in an effort to enrich RCT-derived data and provide physicians with data from patients more broadly resembling those seen in practice.

Our aim was to examine the relationship between burden of disability and disease outcomes in order to evaluate the comparative effectiveness and tolerability of antipsychotics in a real-life setting. As antipsychotic medications are not without attendant risks, clinicians need to be able to strike a favorable balance between the benefits of treatment and the potential risks offered by the wide range of available agents. In this article, we present clinically relevant outcomes such as discontinuation rate, response, relapse, number needed to treat (NNT), emergence of adverse events, and number needed to harm (NNH) based on the pragmatic assessment of 7658 patients in a naturalistic setting.

METHOD

Study Design

The study design has been published in detail previously[12]; however, it is important to reiterate the key elements of this study. IC-SOHO (study code F1D-SN-HGJR) is a prospective, observational study designed to assess the outcomes associated with antipsychotic use in outpatients suffering from schizophrenia. Being that the study was noninterventional, all treatment was at the discretion of the psychiatrist, including flexible dosing and use of concomitant therapies and medications. Investigators were able to prescribe any commercially available antipsychotic medication indicated for the treatment of patients suffering from schizophrenia in their country. No medications were provided by the study sponsor. The primary objective of the study was to understand the costs and outcomes of therapy for schizophrenia with olanzapine compared with other antipsychotics. Patients were assessed at study entry (baseline) and 3, 6, 12, 18, 24, 30, and 36 months postbaseline. Each postbaseline assessment visit had a suggested 1-month visit window on either side of the scheduled timing; however, as this was an observational study, data were considered evaluable if collected within 0 to 6 months for the 3-month visit, within 3 to 12 months for the 6-month visit, and within a 12-month window for all remaining visits, so long as the visits were in chronological order. The study was approved and conducted in accordance with local (country) ethics and regulatory requirements; all patients consented to participate. Investigators were trained to use the study assessment tools and familiarize them with the study requirements; however, no formal assessment of interrater reliability was conducted.

To facilitate comparisons between specific antipsychotic therapies, post hoc analysis cohorts based on the antipsychotic patients were initiated on or switched to at study entry were established. Here, we report data from the most commonly prescribed antipsychotic monotherapies (olanzapine, risperidone, quetiapine, and haloperidol), with an emphasis on patients who maintained their baseline antipsychotic monotherapy. Although prescription of clozapine was also relatively common (N = 237 at baseline), these patients were not included in the analysis as they represent a different patient subgroup.

Patient Population

Only 3 inclusion criteria were applied: whether the patient initiated or changed to olanzapine or nonolanzapine antipsychotic medication at study entry in an outpatient, ambulatory, or community setting (or in hospital during an admission scheduled for the initiation or change, maximum hospitalization period of 2 weeks); had a new or confirmed a diagnosis of schizophrenia according to the DSM-IV[13] or ICD-10[14] criteria for schizophrenia; and was at least 18 years of age. All patients meeting these criteria were considered eligible so long as they were not participating in another study that included a treatment intervention and/or an investigational drug. Patients were enrolled from 27 countries across 4 continents (Africa, the Middle East, Asia, Latin America, Central and Eastern Europe) during the period November 2000 to December 2001, using a nonrandomized process that alternated between 2 groups. Group 1 consisted of patients initiating or changing to olanzapine, and group 2 consisted of patients initiating or changing to nonolanzapine medication therapy. After the first patient was enrolled in group 1, enrollment alternated until 10 patients were enrolled (5 in each group). This deliberate oversampling of olanzapine patients was done in order to facilitate comparisons between the 2 groups, as per the primary objective.

Measures and Definitions

As this was a naturalistic study, we sought to preserve the flexibility of routine clinical care while allowing the evaluation of relevant outcomes in a meaningful way. The assessment tools were based on use of either physician evaluations or patient reports and were chosen for simplicity, ease of training, and ease of use, including the need for translation. The primary clinical measure was the Clinical Global Impressions Severity Scale–Schizophrenia version (CGI-SCH).[15] In addition to overall symptomatology, this adaptation of the original Clinical Global Impressions scale also scores positive, negative, depressive, and cognitive subdomains on a scale from 0 (normal) to 7 (among the most severely ill). Patients were classed as "treatment responders" if their overall CGI-SCH score decreased by at least 2 points from baseline (if their baseline overall CGI-SCH score was ≥ 4) or if they had an overall CGI-SCH score at least 1 point lower than baseline (if their baseline overall CGI-SCH score was 3). Given their minimal symptomatology, patients with a baseline overall CGI-SCH score of 1 or 2 were excluded from the analysis of response. Treatment responders who experienced a worsening of symptoms were considered to have "relapsed" if they had a postresponse overall CGI-SCH score of equal or worse severity than their baseline overall CGI-SCH score, or if their overall CGI-SCH score increased by at least 2 points from the lowest recorded overall CGI-SCH score. Once patients relapsed, they were not subsequently classified as responders. All-cause treatment discontinuation includes patients known to have discontinued treatment (those who stopped using their original baseline antipsychotic, or added another antipsychotic, or switched to another antipsychotic) and patients who were lost to follow-up or had missing drug information. Patients who maintained their baseline antipsychotic monotherapy prescription throughout the 36-month study were considered to be monotherapy "treatment completers." For some comparisons, an NNT(H) approach was used. This method is increasingly prevalent in the psychiatric literature as a valuable measure that allows the clinician to assess the comparative potential risks associated with treatment in a clinically meaningful way. More specifically, NNT(H) estimates the number of patients who would require treatment with agent A instead of agent B in order to achieve 1 additional positive (or negative) outcome, such that the smaller the absolute magnitude of NNT(H), the greater the difference between the 2 treatments.[16,17]

Antipsychotic medication use in the 6 months prior to enrollment was recorded at study entry, in addition to the antipsychotics prescribed upon presentation to each visit (drug name, formulation, and dosage) and those prescribed at the visit, including the reasons for treatment initiation or change. Modifications to antipsychotic therapy were documented separately for changes made prior to and during the visit. Physicians were asked to select all applicable reasons from the following options: not applicable (no modification made), lack of or incomplete effectiveness with the medication therapy, intolerability to the medication therapy, lack of or incomplete compliance/adherence with the medication therapy, and patient's request. Concomitant medications in use at the time of the assessment visit and those prescribed at the visit were documented by medication class (anticholinergics, antidepressants, anxiolytics/hypnotics, mood stabilizers). Patient history was taken at baseline; sociodemographic, behavioral, and health service use information was recorded at each study visit.

Extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) judged to be associated with antipsychotic medication therapy were assessed by the physician at each study visit using a 4-point scale: not present; present, but do not significantly interfere with patient's functioning or health-related quality of life; present, and significantly interferes with patient's functioning or health-related quality of life; and present, and outweighs therapeutic effect. The last 3 classifications were collapsed to "present" and compared with "not present." These scales are based on the UKU Side Effects Rating Scale, which recommends assessment of individual symptoms using a 4-point scale, where the points represent not present/normal, mild, moderate, or severe symptoms.[18] Patients were asked to rate their sexual functioning in the 4 weeks prior to assessment by indicating the most relevant statement: "I had no problems with sexual function," "I had some problems with sexual function," or "I have been unable to perform

sexually." The last 2 choices were combined to achieve a binary outcome.

Statistics

A priori comparisons were between patients who initiated or changed to olanzapine (group 1) and patients who initiated or changed to nonolanzapine medication therapy (group 2). The sample size calculation was based on a 90% power, an α level of .05, the assumption of a 139% variance in mean costs, and the assumption that 50% of patients or their data will not be available for analyses at 3 years. This estimated that a minimum of 2800 patients per group were needed to detect a mean cost difference of 17%.

Cohorts based on the antipsychotics patients were initiated on or switched to at study entry were established for use in this analysis. Patients had to have remained on monotherapy olanzapine, risperidone, quetiapine, or haloperidol for at least 3 months and were included in the analysis for as long as they maintained their initial monotherapy treatment.

Descriptive statistics were used to characterize patients at study entry, and comparisons across treatment groups were made using analysis of variance or logistic regression. In all comparisons of postbaseline data, differences were adjusted for a set of available covariates selected a priori to minimize the potential confounding in estimating treatment effects. These covariates were selected based on clinical expectations that they may be associated with patient outcomes. The covariates used for adjustment included age, gender, duration of diagnosis, overall baseline CGI-SCH scores, prior use of depot typical antipsychotics, prior use of clozapine, and hospitalization in the 6 months prior to baseline. In comparisons against a single reference, olanzapine is used as the reference group reflecting the a priori olanzapine and nonolanzapine treatment groups.

Time until treatment discontinuation, response, and relapse were estimated by Kaplan-Meier survival curves. The survival probabilities at 36 months were used to calculate the NNT[19] (except for relapse, for which the probabilities at 30 months have been used). Cox proportional hazards regression models that adjusted for the covariates listed above were used, and results are reported as hazard ratios and 95% confidence intervals.

Treatment-emergent adverse events were compared with marginal models using generalized estimating equations[20] that adjusted for the a priori fixed covariates listed above, plus time classified into months (3, 6, 12, 18, 24, 30, and 36). Models used an unstructured working correlation matrix. Patients with the adverse event present at baseline were not included in the model.

All statistical analyses were performed using SAS software version 8.02 for Windows (SAS Institute, Cary, N.C.). No adjustment for multiple comparisons was performed, but the level of statistical significance was defined a priori as a 2-sided p value of .001.

RESULTS

Patient Characteristics

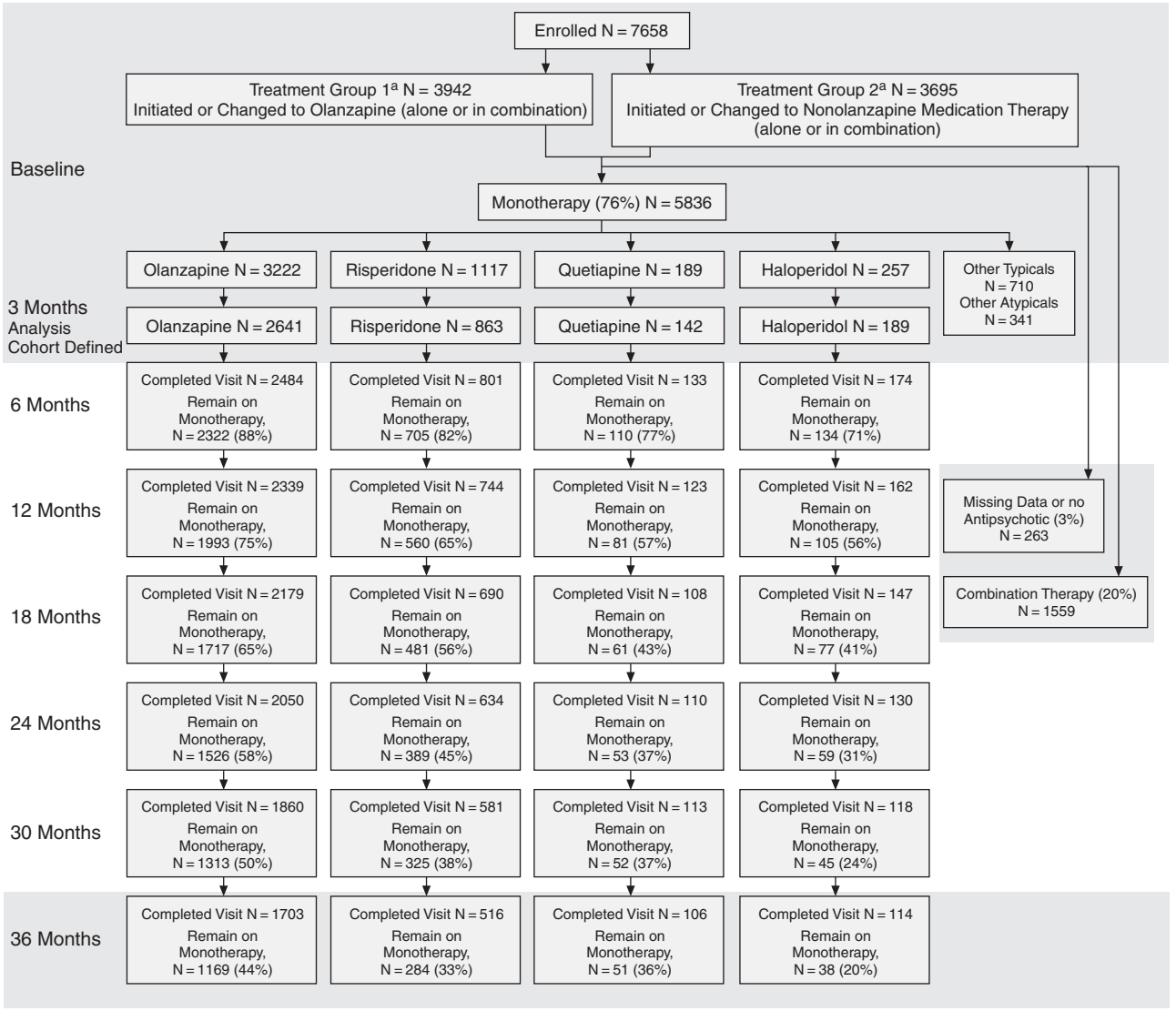
Of the 7637 patients prescribed antipsychotics at baseline, the majority of patients (76%) received antipsychotic monotherapy (Figure 1). Analysis cohorts based on the most commonly prescribed antipsychotic monotherapies were defined at the first postbaseline visit (3 months); patient retention rates varied across these treatment cohorts, as shown in Figure 1, and there was a temporal decline in patient numbers for all groups.

Patient demographic, clinical, and functional characteristics at study entry (baseline) are described in Table 1. To assess the validity of the remain-on-monotherapy treatment groupings, comparisons across those who "completed" 36 months of treatment with their baseline monotherapy and those who changed/modified their baseline monotherapy during the study (including those who discontinued their baseline antipsychotic in the first 3 months) were also included.

Overall, 20% of patients (N = 950) discontinued their baseline monotherapy prior to the 3-month study visit (Table 1). Compared with patients who remained on their original monotherapy, patients who discontinued early reported fewer events of EPS (33% vs. 38%, p = .002) and sexual dysfunction (46% vs. 51%, p = .011), but were not as socially active (54% vs. 59%, p = .002). None of these differences reached statistical significance, but in each case, there was a 5% difference between the groups, suggesting potential clinical relevance (Table 1). When the remain-on-monotherapy cohort (N = 3835) was divided on the basis of whether or not patients maintained their baseline antipsychotic prescription throughout the entire study (40% did and were classed as monotherapy completers), there was a statistically significant difference in only 1 characteristic—significantly more patients who completed the study had EPS at baseline (43% vs. 36%, p < .001). As was seen in those patients who discontinued in the first 3 months, sexual dysfunction was comparatively less prevalent in noncompleters (49% vs. 54%, p = .006). There were no other noteworthy differences based on treatment completion status.

Patients in the monotherapy treatment cohorts shared similar characteristics, although there were some important differences, particularly in the quetiapine and haloperidol groups. Compared with the atypical groups, haloperidol patients were, on average, more likely to have had an inpatient admission in the 6 months prior to the study and experienced greater occupational and social dysfunction (less likely to have a partner or spouse, paid employment, or independent housing or be socially active). They were however, significantly less depressed than patients

Figure 1. Patient Flowchart Outlining the Analysis Cohorts and Patient Numbers Across the 3-Year Observation Period



[a]N=21 missing data.

in the other treatment groups (Table 1). Patients in the quetiapine group were distinguished by a relatively greater proportion of women, a lower proportion of patients receiving an antipsychotic for schizophrenia for the first time, and a high prevalence of sexual dysfunction and antidepressant use. Of all the treatment cohorts, those prescribed quetiapine were the least compromised in terms of social and occupational status.

Dosing

Dosing was relatively consistent throughout the study, although there were differences across the treatment groups, with quetiapine the most variable. The median olanzapine dose was 10 mg/day throughout the study; the mean daily dose in milligrams (standard deviation [SD]) ranged from 9.8 (4.0) at baseline to 10.8 (4.8) at 12 months. The median prescribed dose of risperidone was 3 mg/day at baseline; however, by 3 months, this had risen to 4 mg/day and was maintained at 4 mg/day for the duration of the study. The mean daily dose (SD) ranged between 3.5 (1.8) at baseline and 4.1 (2.2) at 18 and 36 months. The median haloperidol dose was 10 mg/day prior to 36 months, when it dropped to 7.5 mg/day; mean daily dose (SD) ranged from 10.5 (8.8) at 24 months to 12.2 (9.6) at 6 months. Quetiapine was initially prescribed at a median daily dose of 200 mg, which rose to 300 mg at 3 months and further increased to 400 mg at 24 months before dropping back to 362.5 mg at 36 months. During this time, the mean daily dose (SD) ranged from 241.9 (166.0) at baseline to 370.7 (189.8) at 30 months. These

Table 1. Baseline Demographic, Clinical, and Functional Characteristics of Monotherapy Patients by Baseline Monotherapy Status, Treatment Cohort, and Treatment Completion Status

Characteristic	Prescribed Monotherapy at Baseline[a] (N = 4785)			Remain on Monotherapy[c] (N = 3835)					Treatment Completers/Noncompleters[d] (N = 3835)		
	Discontinued[b] Before 3 Mo	Remain on Monotherapy	p Value	Olanzapine	Risperidone	Quetiapine	Haloperidol	p Value	Completers	Noncompleters	p Value
N	950	3835	…	2641	863	142	189	…	1542	2293	…
Proportion of all patients (N = 7658), %	12.4	50.1	…	34.5	11.3	1.9	2.5	…	20.1	29.9	…
Demographics											
Gender, women, %	45.2	46.3	.551	45.2	48.1	54.6	47.1	.095	46.7	46.0	.684
Age, mean (SD), y	34.9 (11.9)	35.1 (12.2)	.536	34.8 (12.2)	36.0 (12.3)	35.6 (12.2)	35.1 (11.4)	.101	35.4 (12.1)	35.0 (12.2)	.342
Clinical status											
Duration of illness,[e] mean (SD), y	8.5 (9.8)	8.8 (9.8)	.402	8.6 (9.7)	9.2 (10.1)	9.6 (10.8)	9.4 (9.6)	.227	8.8 (9.5)	8.8 (10.1)	.979
Never received an antipsychotic for schizophrenia, %	16.2	17.9	.220	18.1	18.1	11.3	19.0	.232	16.3	19.0	.036
Schizophrenia-related admission to an inpatient facility (past 6 mo), %	34.0	34.4	.790	34.8	31.9	30.1	44.9	.007	33.2	35.3	.201
CGI-SCH score, mean (SD)											
Overall	4.4 (1.0)	4.3 (1.1)	.151	4.4 (1.1)	4.2 (1.1)	4.3 (1.1)	4.3 (1.1)	.013	4.3 (1.1)	4.3 (1.1)	.134
Positive	4.0 (1.4)	3.9 (1.4)	.012	3.9 (1.4)	3.9 (1.4)	3.8 (1.5)	4.2 (1.3)	.058	3.8 (1.4)	4.0 (1.4)	.002
Negative	3.8 (1.3)	4.0 (1.3)	.006	4.0 (1.3)	3.9 (1.3)	4.1 (1.4)	3.8 (1.4)	.061	3.9 (1.3)	4.0 (1.3)	.765
Depressive	3.2 (1.4)	3.3 (1.4)	.002	3.4 (1.4)	3.2 (1.3)	3.5 (1.4)	2.9 (1.3)	< .001	3.3 (1.4)	3.3 (1.4)	.808
Cognitive	3.6 (1.4)	3.7 (1.4)	.058	3.7 (1.4)	3.6 (1.4)	3.7 (1.3)	3.6 (1.3)	.617	3.7 (1.3)	3.7 (1.4)	.535
Extrapyramidal symptoms, % at baseline	33.0	38.4	.002	38.7	39.5	34.8	31.5	.173	42.5	35.6	< .001
Tardive dyskinesia, % at baseline	5.6	7.8	.026	7.8	8.1	7.9	6.0	.820	7.6	7.9	.803
Sexual dysfunction, patient perception, % at baseline	46.0	50.8	.011	51.5	48.5	60.5	44.5	.022	53.7	48.9	.006
Concomitant medications, % use at baseline											
Anticholinergics	30.4	32.2	.291	30.9	35.0	35.9	35.4	.070	33.9	31.1	.073
Antidepressants	16.3	17.9	.262	18.5	16.2	25.4	11.1	.004	19.5	16.8	.035
Anxiolytics/hypnotics	32.4	35.2	.107	36.4	32.1	33.1	34.4	.133	34.7	35.5	.590
Mood stabilizers	9.3	10.0	.503	10.9	8.7	6.3	5.8	.022	9.4	10.4	.323
Functional status											
Involved in a spouse/partner relationship (today), %	36.3	36.2	.967	35.8	38.0	45.1	26.9	.006	35.1	36.9	.268
Paid employment (past 4 wk), %	17.2	20.4	.026	20.6	20.8	23.4	13.8	.113	20.3	20.5	.906
Living independently (past 4 wk), %	33.5	32.9	.727	32.9	33.3	40.4	27.1	.091	34.6	31.9	.081
Social activities outside of the primary relationship (past 4 wk), %	53.7	59.2	.002	59.2	60.7	63.6	49.7	.033	58.9	59.4	.772

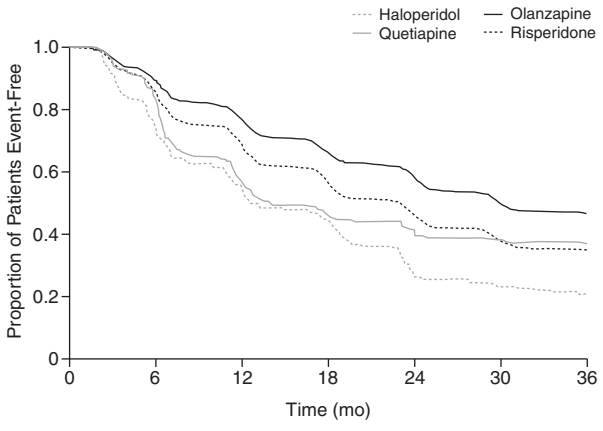
[a]Patients who were prescribed olanzapine, risperidone, quetiapine, or haloperidol as their baseline antipsychotic monotherapy.
[b]Patients were considered to have discontinued treatment if they stopped using their original baseline antipsychotic or added or switched to another antipsychotic. In addition, this group also includes patients who potentially discontinued, that is, were lost to follow-up or had missing drug information.
[c]Patients who maintained their baseline antipsychotic monotherapy prescription for at least 3 months (analysis cohort).
[d]Completers = patients who maintained their baseline antipsychotic monotherapy prescription throughout the study (36 months). Noncompleters = patients who met the definition of remain on monotherapy, but switched treatment within 36 months. Treatment completion status is shown only for those patients in the remain on monotherapy cohort (N = 3835, see footnote c).
[e]Calculated from age of the patient at the first service contact for schizophrenia.
Abbreviation: CGI-SCH = Clinical Global Impressions Severity Scale–Schizophrenia version.

Table 2. Rates, Median Time to Discontinuation, Comparative Risk, and Number Needed to Treat (NNT) for All-Cause Treatment Discontinuation Across Treatment Groups for Patients Remaining on Monotherapy Treatment [a,b]

Result	Olanzapine (N = 2641)	Risperidone (N = 863)	Quetiapine (N = 142)	Haloperidol (N = 189)
Patients discontinued, % (N)[c]	56 (1472)	67 (579)	64 (91)	80 (151)
Kaplan-Meier median time to discontinuation (95% CI), mo	30.0 (29.3 to 30.7)	23.1 (18.6 to 23.9)	13.9 (11.6 to 23.9)	12.5 (11.2 to 18.2)
Olanzapine as reference				
Hazard ratio (95% CI)	…	1.4 (1.3 to 1.6)	1.5 (1.2 to 1.8)	2.2 (1.9 to 2.6)
p Value	…	< .001	< .001	< .001
NNT (95% CI)				
18 mo	…	11 (8 to 18)	5 (4 to 10)	5 (4 to 8)
36 mo	…	9 (7 to 13)	11 (6 to 124)	4 (4 to 6)
Risperidone as reference				
Hazard ratio (95% CI)	…	…	1.1 (0.8 to 1.3)	1.6 (1.3 to 1.9)
p Value	…	…	.65	< .001
NNT (95% CI)				
18 mo	…	…	9 (5 to 62)	9 (6 to 29)
36 mo	…	…	–42 (16 to –9)	8 (5 to 14)
Quetiapine as reference				
Hazard ratio (95% CI)	…	…	…	1.5 (1.1 to 2.0)
p Value	…	…	…	.005
NNT (95% CI)				
18 mo	…	…	…	113 (9 to –10)
36 mo	…	…	…	6 (4 to 16)

[a]A negative value for NNT should be considered as a number needed to harm (NNH). When the comparison is not statistically significant, the confidence interval for the absolute risk reduction will include zero, thus the 95% confidence interval for the NNT/NNH will include infinity, as well as positive and negative values.
[b]Results have been adjusted for baseline variables (duration of disease, use of typicals and/or clozapine in the past 6 months, hospitalization in the past 6 months, gender, age, and overall Clinical Global Impressions Severity Scale–Schizophrenia version score).
[c]Patients were considered to have discontinued treatment if they stopped using their original baseline antipsychotic or added or switched to another antipsychotic. In addition, this group also includes patients who potentially discontinued, that is, were lost to follow-up or had missing drug information.

Figure 2. Kaplan-Meier Estimates of the Time to All-Cause Treatment Discontinuation[a,b]



[a]$p < .001$ for olanzapine vs. risperidone, quetiapine, and haloperidol, and $p < .001$ for risperidone vs. haloperidol.
[b]Patients censored from each treatment group: olanzapine N = 1125, risperidone N = 273, quetiapine N = 50, and haloperidol N = 35. Patients were considered to have discontinued treatment if they stopped using their original baseline antipsychotic or added or switched to another antipsychotic. In addition, this group also includes patients who potentially discontinued, that is, were lost to follow-up or had missing drug information.

data represent both oral and depot formulations where appropriate.

All-Cause Treatment Discontinuation

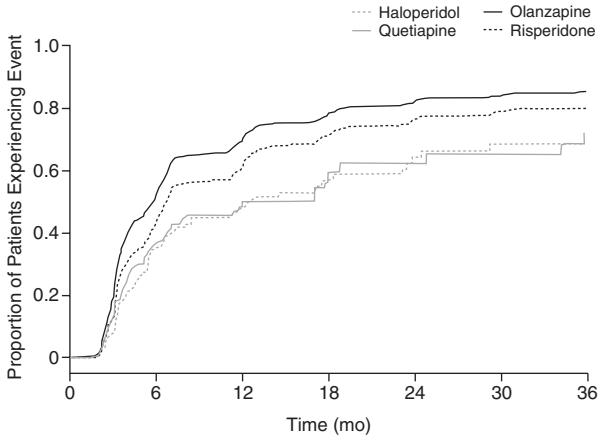
Three-year all-cause treatment discontinuation rates ranged from 56% for olanzapine to 80% for haloperidol (Figure 2). Patients who were switched to or initiated on treatment with haloperidol were most at risk of discontinuing their baseline monotherapy, being 2.2 times more likely to discontinue than olanzapine patients ($p < .001$), 1.6 times more likely than risperidone patients ($p < .001$), and 1.5 times more likely than quetiapine patients ($p = .002$). Of the atypical agents, patients switched to or initiated on treatment with olanzapine appeared to fare comparatively better. Olanzapine was associated with the lowest risk of discontinuation ($p < .001$ compared with all other therapies). The median time to discontinuation also varied across treatments, from 30 and 23 months for olanzapine and risperidone, respectively, to 14 and 13 months for quetiapine and haloperidol, respectively (Table 2). The NNT analysis places these findings into a more clinical context, indicating a comparative advantage for olanzapine in terms of prevention of all-cause treatment discontinuation, with NNTs ranging from 5 to 11 at 18 months and 4 to 11 at 36 months (Table 2). Risperidone also

Table 3. Proportion of Patients Who Responded to Treatment While on Antipsychotic Monotherapy, Median Time to Achieve This Response, Comparative Risk of Response, and Number Needed to Treat (NNT) Across Treatment Groups for Patients Remaining on Monotherapy Treatment[a,b]

Result	Olanzapine (N = 2503)	Risperidone (N = 822)	Quetiapine (N = 133)	Haloperidol (N = 179)
Patients responded, % (N)[c]	78 (1945)	65 (530)	47 (62)	48 (85)
Kaplan-Meier median time to response (95% CI), mo	5.2 (5.0 to 5.5)	6.3 (6.0 to 6.7)	11.3 (6.3 to 17.5)	11.7 (6.6 to 17.7)
Olanzapine as reference				
Hazard ratio (95% CI)	…	0.8 (0.7 to 0.8)	0.6 (0.4 to 0.7)	0.5 (0.4 to 0.7)
p Value	…	< .001	< .001	< .001
NNT (95% CI)				
18 mo	…	13 (9 to 25)	6 (4 to 18)	5 (4 to 8)
36 mo	…	15 (10 to 31)	7 (4 to 33)	8 (4 to 50)
Risperidone as reference				
Hazard ratio (95% CI)	…	…	0.8 (0.6 to 1.0)	0.7 (0.6 to 0.9)
p Value	…	…	.037	.004
NNT (95% CI)				
18 mo	…	…	11 (5 to –36)	8 (5 to 24)
36 mo	…	…	12 (5 to –23)	16 (6 to –19)
Quetiapine as reference				
Hazard ratio (95% CI)	…	…	…	1.0 (0.7 to 1.3)
p Value	…	…	…	.737
NNT (95% CI)				
18 mo	…	…	…	24 (6 to –10)
36 mo	…	…	…	–41 (7 to –6)

[a]A negative value for NNT should be considered as a number needed to harm (NNH). When the comparison is not statistically significant, the confidence interval for the absolute risk reduction will include zero, thus the 95% confidence interval for the NNT/NNH will include infinity, as well as positive and negative values.
[b]Results have been adjusted for baseline variables (duration of disease, use of typicals and/or clozapine in the past 6 months, hospitalization in the past 6 months, gender, age, and overall Clinical Global Impressions Severity Scale–Schizophrenia version [CGI-SCH] score).
[c]Patients were considered to have responded to treatment if they met the following criteria: overall CGI-SCH score decreased by at least 2 points from baseline (if the baseline overall CGI-SCH score was ≥ 4), or an overall CGI-SCH score at least 1 point lower than baseline (if the baseline overall CGI-SCH score was 3). Patients with a baseline overall CGI-SCH score of 1 or 2 were excluded from the analysis.

Figure 3. Kaplan-Meier Estimates of the Time to Treatment Response[a,b]



[a]p < .001 for olanzapine vs. risperidone, quetiapine, and haloperidol.
[b]Patients censored from each treatment group: olanzapine N = 537, risperidone N = 284, quetiapine N = 69, and haloperidol N = 92. Patients were considered to have responded to treatment if they met the following criteria: overall Clinical Global Impressions Severity Scale–Schizophrenia version (CGI-SCH) score decreased by at least 2 points from baseline (if the baseline overall CGI-SCH score was ≥ 4), or an overall CGI-SCH score at least 1 point lower than baseline (if the baseline overall CGI-SCH score was 3).

compared favorably with quetiapine and haloperidol at 18 months, with an NNT of 9; however, it appears as though the advantage over quetiapine was lost at 36 months. Low patient numbers at 36 months make these estimates less reliable for the smaller treatment groups.

Treatment Response and Relapse

Irrespective of treatment group, response rates attenuated over time as shown in Figure 3. The majority of patients in the olanzapine and risperidone groups responded to treatment (78% and 65% respectively), whereas less than half the patients receiving quetiapine or haloperidol met the criteria for treatment response (47% and 48%) within the 36-month observation period (Table 3). Further, for those patients who did respond, olanzapine and risperidone patients did so more rapidly than quetiapine or haloperidol patients (median response times of 5 and 6 months compared with 11 and 12 months). The NNT estimates further highlight the differences between the treatment groups. NNTs of 5 to 8 for olanzapine versus quetiapine and haloperidol demonstrate benefits in terms of achieving treatment response (Table 3).

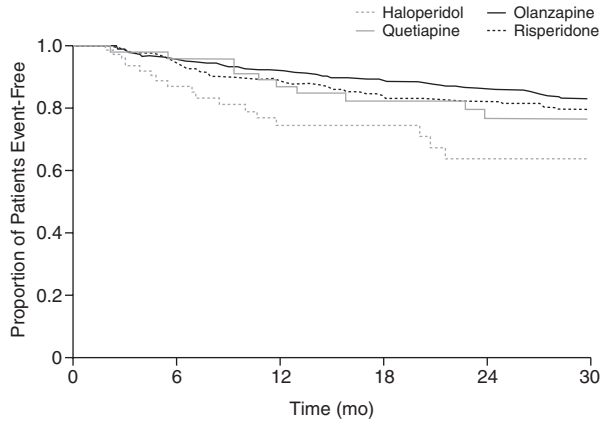
Patients considered to be treatment responders within the first 30 months of observation were further analyzed to determine relapse rates (Figure 4). The proportion of

Table 4. Proportion of Patients Who Relapsed Following Treatment Response, Comparative Risk of Relapse, and Number Needed to Treat (NNT) Across Treatment Groups for Patients Remaining on Monotherapy Treatment[a]

Result	Olanzapine (N = 2641)	Risperidone (N = 863)	Quetiapine (N = 142)	Haloperidol (N = 189)
Patients responded, % (N)[b]	74 (1945)	61 (530)	44 (62)	45 (85)
Patients responded up to 30 mo, N[c]	1933	529	62	83
Patients relapsed, % (N)[d]	12 (227)	14 (73)	18 (11)	20 (17)
Olanzapine as reference				
Hazard ratio (95% CI)	…	1.3 (1.0 to 1.7)	1.7 (0.9 to 3.0)	3.7 (2.2 to 6.1)
p Value	…	.053	.11	< .001
NNT (95% CI)				
18 mo	…	21 (11 to 132)	16 (6 to –21)	7 (4 to 40)
30 mo[e]	…	31 (10 to –24)	16 (5 to –10)	6 (3 to –11)
Risperidone as reference				
Hazard ratio (95% CI)	…	…	1.3 (0.7 to 2.4)	2.8 (1.7 to 4.9)
p Value	…	…	.47	< .001
NNT (95% CI)				
18 mo	…	…	67 (8 to –10)	11 (5 to –34)
30 mo[e]	…	…	32 (5 to –7)	7 (3 to –8)
Quetiapine as reference				
Hazard ratio (95% CI)	…	…	…	2.2 (1.0 to 4.8)
p Value	…	…	…	.039
NNT (95% CI)				
18 mo	…	…	…	13 (5 to –12)
30 mo[e]	…	…	…	8 (3 to –5)

[a]A negative value for NNT should be considered as number needed to harm (NNH). When the comparison is not statistically significant, the confidence interval for the absolute risk reduction will include zero, thus the 95% confidence interval for the NNT/NNH will include infinity, as well as positive and negative values.
[b]Patients were considered to have responded to treatment if they met the following criteria: overall Clinical Global Impressions Severity Scale–Schizophrenia version (CGI-SCH) score decreased by at least 2 points from baseline (if the baseline overall CGI-SCH score was ≥ 4), or an overall CGI-SCH score at least 1 point lower than baseline (if the baseline overall CGI-SCH score was 3). Patients with a baseline overall CGI-SCH score of 1 or 2 were excluded from the analysis.
[c]Those patients who met the criteria for treatment response up to 30 months, with overall CGI-SCH scores ≥ 3, and were thus eligible for inclusion in the analysis of relapse (used as the denominator for calculating relapse rates).
[d]Patients were considered to have relapsed if they met the following criteria: previously met the criteria for response, prior to a reversal in the improvement in overall CGI-SCH score back to baseline severity or worse, or an increase in overall CGI-SCH score of at least 2 from the lowest recorded overall CGI-SCH score. Once patients have relapsed, they cannot subsequently be classified as responders.
[e]Number needed to treat is presented at 30 months to accommodate the requirements of the definition (see footnote c above).

Figure 4. Kaplan-Meier Estimates of the Time to Relapse[a,b]



[a]p < .001 for olanzapine vs. haloperidol, and p < .001 for risperidone vs. haloperidol.
[b]Patients were considered to have relapsed if they met the following criteria: previously met the criteria for response, prior to a reversal in the improvement in overall Clinical Global Impressions Severity Scale–Schizophrenia version (CGI-SCH) score back to baseline severity or worse, or an increase in overall CGI score of at least 2 from the lowest recorded overall CGI-SCH score. Once patients relapsed, they could not subsequently be classified as responders.

patients who relapsed was similar for olanzapine and risperidone (12% and 14%, respectively) and lower than for quetiapine (18%) and haloperidol (20%) (Table 4). Patients on haloperidol monotherapy were 3.7 times and 2.8 times more likely to experience symptom relapse than those receiving olanzapine or risperidone, respectively (p < .001), and were 2.2 times more likely to relapse than quetiapine patients (p = .039). The NNT estimates indicate that olanzapine is comparatively more favorable than haloperidol in terms of relapse prevention, with estimates of 7 and 6 at 18 and 30 months, respectively (Table 4). This analysis is derived from patients who responded and then relapsed, so patient numbers are very low in the quetiapine and haloperidol groups, making comparisons less precise.

Concomitant Medications

Prescription of concomitant medications was common throughout the study, with 80% of patients prescribed 1 or more medications at some point. Patients on haloperidol monotherapy were significantly more likely (p < .001) to require anticholinergic drugs (94% of patients) than patients receiving quetiapine (20% of patients, odds ratio

[95% CI] = 60.2 [22.9 to 157.8]), olanzapine (23%, 49.8 [24.0 to 103.5]), or risperidone (71%, 5.9 [2.8 to 12.4]). Among patients receiving atypicals, those on quetiapine or olanzapine monotherapy were less likely ($p < .001$) to require anticholinergics than those receiving risperidone (quetiapine vs. risperidone, 0.10 [0.05 to 0.19]; quetiapine vs. haloperidol, 0.02 [0.01 to 0.04]; olanzapine vs. risperidone, 0.12 [0.09 to 0.15]; olanzapine vs. haloperidol, 0.02 [0.01 to 0.04]).

Antidepressant use during the study was highest for haloperidol patients (62%, compared with olanzapine, 42%; odds ratio [95% CI] = 2.7 [1.6 to 4.5], $p < .001$; compared with quetiapine, 58%; 1.5 [0.7 to 2.9], $p = .287$; compared with risperidone, 50%; 2.0 [1.2 to 3.4], $p = .014$) and lowest for those taking olanzapine (vs. risperidone, 0.74 [0.59 to 0.92], $p = .007$; vs. quetiapine, 0.54 [0.33 to 0.89], $p = .015$). Similarly, patients on haloperidol monotherapy were more likely to be prescribed anxiolytics or hypnotics (87%) than patients receiving olanzapine (58%, 4.8 [2.7 to 8.4], $p < .001$), quetiapine (63%, 4.2 [2.0 to 8.6], $p < .001$), or risperidone (72%, 2.6 [1.4 to 4.7], $p = .002$). Further, olanzapine-treated patients were less likely to use anxiolytic or hypnotic medications than risperidone-treated patients (0.54 [0.43 to 0.67], $p < .001$).

Mood stabilizers were the least frequently prescribed concomitant medications in IC-SOHO. Coprescription rates of mood stabilizers were similar for patients on olanzapine and risperidone monotherapies (olanzapine vs. risperidone, 25% vs. 29%, 0.82 [0.63 to 1.1], $p = .151$), slightly lower for quetiapine-treated patients (19%), and highest for those receiving haloperidol monotherapy (46% compared with olanzapine 2.5 [1.4 to 4.3], $p = .001$; risperidone 2.1 [1.1 to 3.7], $p = .016$; and quetiapine 3.6 [1.5 to 8.5], $p = .003$).

Tolerability

Patients on all antipsychotic monotherapies experienced treatment-emergent adverse events; however, the risk profile differed for each antipsychotic (Table 5). The odds of treatment-emergent EPS and TD were highest for patients on haloperidol monotherapy ($p \leq .002$), producing NNH estimates of 3 versus olanzapine and quetiapine and 5 versus quetiapine for EPS. Among patients receiving atypical antipsychotics, risperidone patients experienced significantly greater odds of developing EPS than olanzapine ($p < .001$) or quetiapine ($p < .001$) patients and were at significantly greater risk of developing TD than olanzapine patients ($p < .001$). Patients taking quetiapine were less likely to develop EPS than those on olanzapine monotherapy ($p = .015$). Patients in the risperidone group experienced significantly greater odds ($p < .001$) of developing sexual dysfunction during treatment compared with olanzapine patients. A similar trend was observed for haloperidol patients compared with olanzapine patients ($p = .004$). Olanzapine patients were at significantly higher risk of clinically significant weight gain of more than 7% of baseline body weight compared with all other antipsychotics examined ($p < .001$); NNH estimates range from 7 to 18 depending on the comparator and duration of treatment (Table 5).

DISCUSSION

Debate over the credibility of observational data still exists, despite an improved understanding of the value they provide and evidence suggesting good concordance with RCT data.[21] At least some of this contention may be related to the poor reporting of these trials, although this is not restricted to such trials, as evidenced by Cochrane review of 2000 controlled schizophrenia trials.[22] With this in mind, where possible, we have tried to adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational data.[23,24]

The strength of noninterventional naturalistic studies lies in their ability to reveal how patients are treated, and how they respond to such treatment in a clinical practice setting. In the IC-SOHO cohort, antipsychotics were most commonly prescribed as single therapies. By following the most frequently prescribed monotherapy treatment cohorts for up to 3 years, we were able to explore long-term benefits and potential risks during antipsychotic treatment and identify significant differences in outcomes for these relatively young, moderately ill patients initiating or switching antipsychotic therapy. The importance of individualizing treatment for a chronic condition such as schizophrenia is reinforced by our finding that not all patients met the criteria for treatment response (particularly those receiving haloperidol and quetiapine), despite staying on treatment with their original antipsychotic, and that even those responsive to treatment were at significant risk of relapse, as frequently as 1 in 5 for patients on haloperidol monotherapy. Given the flexibility of the study design, physicians were at liberty to change a patient's medication regimen as they saw fit, and, indeed, many patients discontinued the antipsychotic monotherapy they were prescribed at study entry, particularly in the first 6 months of the study. As the allocation of patients to treatment was a discretionary process based on the clinical judgment of the recruiting psychiatrists, rather than the result of randomization, it was important to describe the patients at study entry and look for differences across the treatment groups. The comparatively lower rate of quetiapine prescription for patients receiving their first antipsychotic for schizophrenia may have been due to a lack of experience with this antipsychotic, which was new to the market during the recruitment phase of the study. Prescription of haloperidol to patients with a history of nonadherence, recent hospital admission, and comparatively poor social

Table 5. Emergence of Adverse Events During Antipsychotic Monotherapy: Postbaseline Incidence at Any Time During Treatment, Comparative Risk, and Number Needed to Treat (NNT) for Prevention of an Adverse Event[a,b]

Adverse Event	Risperidone	Quetiapine	Haloperidol
EPS[c]			
Olanzapine as reference			
Adjusted odds (95% CI)	5.63 (4.27 to 7.40)	0.23 (0.07 to 0.75)	16.01 (10.87 to 23.57)
p Value	< .001	.015	< .001
NNT (95% CI)			
18 mo	6 (5 to 7)	–18 (–43 to –12)	3 (3 to 4)
36 mo	5 (5 to 7)	–18 (–57 to –11)	3 (3 to 4)
Risperidone as reference			
Adjusted odds (95% CI)	…	0.04 (0.01 to 0.13)	2.85 (1.93 to 4.20)
p Value	…	< .001	< .001
NNT (95% CI)			
18 mo	…	–5 (–6 to –4)	5 (4 to 9)
36 mo	…	–4 (–5 to –4)	5 (4 to 10)
Quetiapine as reference			
Adjusted odds (95% CI)	…	…	69.52 (20.72 to 233.3)
p Value	…	…	< .001
NNT (95% CI)			
18 mo	…	…	3 (2 to 3)
36 mo	…	…	3 (2 to 3)
Tardive dyskinesia[c]			
Olanzapine as reference			
Adjusted odds (95% CI)	4.15 (2.37 to 7.27)	1.37 (0.39 to 4.72)	11.91 (6.13 to 23.14)
p Value	< .001	.623	< .001
NNT (95% CI)			
18 mo	46 (28 to 121)	403 (42 to –52)	13 (9 to 28)
36 mo	42 (26 to 105)	138 (30 to –53)	10 (7 to 20)
Risperidone as reference			
Adjusted odds (95% CI)	…	0.33 (0.09 to 1.16)	2.87 (1.48 to 5.58)
p Value	…	.084	.002
NNT (95% CI)			
18 mo	…	–52 (185 to –23)	18 (10 to 80)
36 mo	…	–59 (81 to –22)	14 (8 to 39)
Quetiapine as reference			
Adjusted odds (95% CI)	…	…	8.72 (2.39 to 31.83)
p Value	…	…	.001
NNT (95% CI)			
18 mo	…	…	13 (8 to 35)
36 mo	…	…	11 (7 to 26)
Sexual dysfunction[d]			
Olanzapine as reference			
Adjusted odds (95% CI)	2.14 (1.70 to 2.70)	1.43 (0.78 to 2.60)	1.88 (1.23 to 2.88)
p Value	< .001	.246	.004
NNT (95% CI)			
18 mo	10 (7 to 21)	–28 (13 to –7)	19 (7 to –27)
36 mo	10 (7 to 22)	39 (7 to –10)	18 (7 to –27)
Risperidone as reference			
Adjusted odds (95% CI)	…	0.67 (0.36 to 1.23)	0.88 (0.56 to 1.37)
p value	…	.196	.563
NNT (95% CI)			
18 mo	…	–8 (–62 to –4)	–22 (19 to –7)
36 mo	…	–14 (17 to –5)	–24 (17 to –7)
Quetiapine as reference			
Adjusted odds (95% CI)	…	…	1.32 (0.65 to 2.69)
p Value	…	…	.448
NNT (95% CI)			
18 mo	…	…	11 (5 to –19)
36 mo	…	…	31 (6 to –9)

(continued)

Table 5 (continued). Emergence of Adverse Events During Antipsychotic Monotherapy: Postbaseline Incidence at Any Time During Treatment, Comparative Risk, and Number Needed to Treat (NNT) for Prevention of an Adverse Event[a,b]

Adverse Event	Risperidone	Quetiapine	Haloperidol
Weight gain > 7% compared with baseline			
Olanzapine as reference			
Adjusted odds (95% CI)	0.63 (0.54 to 0.73)	0.51 (0.35 to 0.74)	0.50 (0.36 to 0.68)
p Value	< .001	< .001	< .001
NNT (95% CI)			
18 mo	–12 (–25 to –8)	–8 (–138 to –5)	–7 (–16 to –4)
36 mo	–18 (131 to –9)	–9 (48 to –4)	–8 (49 to –4)
Risperidone as reference			
Adjusted odds (95% CI)	…	0.81 (0.55 to 1.21)	0.80 (0.57 to 1.11)
p Value	…	.300	.177
NNT (95% CI)			
18 mo	…	–28 (10 to –6)	–13 (14 to –5)
36 mo	…	–18 (12 to –5)	–14 (12 to –5)
Quetiapine as reference			
Adjusted odds (95% CI)	…	…	0.98 (0.61 to 1.59)
p Value	…	…	.938
NNT (95% CI)			
18 mo	…	…	–25 (7 to –5)
36 mo	…	…	–56 (6 to –5)

[a]A negative value for NNT should be considered as number needed to harm (NNH). When the comparison is not statistically significant, the confidence interval for the absolute risk reduction will include zero, thus the 95% confidence interval for the NNT/NNH will include infinity.
[b]The odds ratios are estimates from a logistic regression model using generalized estimating equations with unstructured covariance structure. The model includes the following baseline covariates: visit, treatment group, age, gender, duration of disease, Clinical Global Impressions Severity Scale–Schizophrenia version overall score, use of depot typical antipsychotics or clozapine in the 6 months prior to enrollment, and hospitalization in the 6 months prior to enrollment.
[c]Physician assessment of symptoms judged to be associated with antipsychotic medication therapy at the assessment visit, based on a 4-point scale: not present; present, but do not significantly interfere with patient's functioning or health-related quality of life; present, and significantly interferes with patient's functioning or health-related quality of life; present, and outweighs therapeutic effect. The last 3 classifications were collapsed to "present" and compared with "not present."
[d]Patient-reported sexual dysfunction in the 4 weeks prior to the visit, based on a 3-point scale: no problems, some problems with sexual function, unable to perform sexually. The last 2 items were collapsed to "yes" or "no" for this analysis.
Abbreviation: EPS = extrapyramidal symptoms.

and functional status may, at least in part, be due to the availability of a depot formulation and the comparatively low cost of this medication compared with atypicals. The absence of large differences between patients in terms of treatment completion status (that is, those patients who discontinued before 3 months vs. those who did not, and "completers" vs. "noncompleters") is reassuring and suggests that patients who remain on monotherapy are representative of the study cohort.

Time to all-cause treatment discontinuation is widely acknowledged as a valuable measure of treatment effectiveness that captures both patient and physician evaluation of the comparative benefits and potential risks of antipsychotic medication therapy, and it has gained importance as the primary outcome measure used in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a U.S. National Institutes of Health–sponsored double-blind clinical trial comparing the effectiveness of antipsychotics.[25] These IC-SOHO data support the CATIE phase I finding that patients receiving olanzapine monotherapy maintain their treatment significantly longer than patients on risperidone or quetiapine; however, even at 36 months, the IC-SOHO discontinuation rates were consistently lower than those observed over 18 months in CATIE. In addition, we also saw significant differences between the atypicals and the typical comparator haloperidol, a differentiation that was not seen in CATIE with the typical comparator perphenazine. The median times to discontinuation were also much greater in IC-SOHO compared with CATIE (4.6 to 9.2 months). Potential factors contributing to these differences include study design (blinded treatments do not allow for patient attitude, a potential modifier of treatment; CATIE patients were randomly assigned to treatment, whereas patients participating in IC-SOHO received their treatment based on the clinical judgment of the physician) and patient characteristics (75% of patients in CATIE were male, with a mean age of 40 years and overall CGI scores of 3.9 to 4.0; none were first-episode patients). Compared with those in IC-SOHO, CATIE patients are a more chronically ill population with greater treatment exposure, requiring higher medication doses and more complex management. The absence of first-episode patients in CATIE is also a notable difference between the 2 studies, with around 17% of patients in IC-SOHO receiving their first antipsychotic prescription.

A recent review of key studies in schizophrenia that included RCTs and observational studies noted that, with some exceptions, discontinuation rates were consistently lowest for clozapine, followed by olanzapine, with

risperidone usually next (when included).[26] Three-year discontinuation rates (36% to 66%, depending on treatment group) have recently been published for one of the studies cited in this review, the Schizophrenia Outpatient Health Outcomes (SOHO) study.[27] IC-SOHO was conducted concurrently with the European SOHO study; however, an intention-to-treat approach and different definition of treatment discontinuation (including only known medication changes) were used, making comparison less straightforward than might be expected.[27] We adopted a more conservative approach to defining all-cause treatment discontinuation and included patients lost to follow-up or with missing data, although sensitivity analyses including data for known discontinuations indicated that the rank order for the atypicals was the same for both studies, despite lower rates for all common treatment groups in IC-SOHO. Comparative dosing and study design suggest that differences between the 2 studies are driven by the patient population, local practice, and analysis approach. The NNT data further facilitate comparison across treatment groups, and our results for olanzapine for prevention of all-cause discontinuation at 18 months were comparable to those seen in CATIE (11 vs. risperidone and 6 vs. quetiapine),[28] suggesting that, in terms of preventing treatment discontinuation, there are real differences between these atypical antipsychotics.

The median daily doses of olanzapine, risperidone, and haloperidol were within the recommended range for the treatment of schizophrenia for each medication. As a new drug to the market, quetiapine was prescribed at potentially suboptimal doses at the beginning of the study, probably due to the need for dose titration; however, dosing increased over time and was within the manufacturer's recommended usual effective dose range of 300 to 450 mg/day by 3 months.[29] A similar prescription pattern was also seen in a naturalistic study conducted in the United States (from 1997 to 2003), in which quetiapine was initially prescribed at a daily dose of 164 mg/day, rising to 330 mg/day at 12 months.[30] There is some evidence to suggest that quetiapine is routinely prescribed in excess of the recommended effective range (the upper limit is 750 or 800 mg/day, depending on the local label)[31,32]; however, at least some of these reports are based on data from inpatients in U.S. state-run psychiatric facilities that report high doses of other antipsychotics also.[31,33,34] As such, it is perhaps unsurprising that our data confirm the effectiveness of quetiapine at lower doses in moderately ill, relatively young outpatients. Indeed, the authors of a recent review concluded that the current evidence suggests that the optimal quetiapine dose is 300 to 400 mg/day,[32] a dose range achieved within 3 months of initiating treatment in IC-SOHO. Importantly, as physicians were free to adjust medication as required at any time, the doses recorded throughout the study reflect the clinical judgment of the physician. Early discontinuations may have been prevented by a more aggressive dosing schedule; however, patients who did well on lower doses maintained their therapy and realized tolerability benefits.

Treatments that reduce symptoms produce important gains in utility, even if they do not induce a complete remission, but they can also lead to the development or exacerbation of other symptoms that further compromise patient outcomes. Data from IC-SOHO provide confirmatory evidence that the long-term tolerability profiles of antipsychotics differ; in particular, that olanzapine patients are at higher risk of clinically significant weight gain (NNH of 8 to 18) and that haloperidol and risperidone patients are at greater risk of impaired motor function (both EPS and TD) and sexual dysfunction. The NNT to prevent 1 case of treatment-emergent TD by using an atypical agent instead of haloperidol ranged from 10 to 18 against haloperidol, highlighting an important limitation of this first-generation treatment. This differential tolerability was also evident in the prescription of concomitant medications.

Coprescription of adjunctive medications was highest for patients on haloperidol monotherapy across all 4 classes of medications examined. Unsurprisingly, given the EPS profile of haloperidol, anticholinergic use was particularly common. In addition, fewer than 15% of haloperidol-treated patients did not require a prescription for anxiolytics, and despite the lowest depression scores at study entry, antidepressants were prescribed to more than two thirds of the patients at some point during the study, suggesting that complex augmentation is required when haloperidol is used as a monotherapy. Among the atypical agents, risperidone was the treatment most commonly coprescribed with anticholinergics and anxiolytics, reflecting the tolerability profile of this agent. The extensive use of antidepressant and anxiolytic/hypnotic medications across all antipsychotic monotherapies suggests that comorbidities such as depression, anxiety, and sleep disturbances are a common feature of illness for this study population.

There are a number of limitations that need to be considered when interpreting these data. As with any observational study, we can only examine associations, not causality. Much emphasis is placed on the absence of randomization and the potential for selection bias in naturalistic studies. Monotherapy groups were used to ensure correct attribution of outcomes, and results were adjusted for baseline covariates of clinical significance; however, the gap between association and causation cannot be bridged by statistical adjustment. It can also be argued that allocation to treatment based on symptoms, patient preference, and physician prescribing practice reflects how drugs are prescribed in the real world and is a key feature of the study. In addition, as per standard clinical practice, raters were not blinded; this may have introduced another potential source of bias. Analysis groups

were defined post hoc, and the primary objective (and recruitment) were based on olanzapine versus nonolanzapine, so there is an imbalance in patient numbers. While this imbalance does not prevent us from comparing the groups, it needs to be recognized that estimates and comparisons involving these groups are less precise than those made with the larger olanzapine and risperidone groups, as indicated by the accompanying confidence intervals. As low precision reduces statistical power, we may have failed to detect meaningful differences in comparisons involving the smaller subgroups. Furthermore, the smaller treatment subgroups may be less representative of the patient population as a whole, thus reducing the external validity of the comparisons. The long duration of the study and ensuing patient dropout led to low numbers of patients in certain subgroups, creating a possible source of attrition bias. Patients had to provide consent and be receiving outpatient care at entry, which restricted the inclusion of severely unwell patients in this sample. However, the 3-year course of observation allowed for long-term follow-up, so at least some of the fluctuating course of illness should have been included. It may also be argued that patients on long-term monotherapy are a self-selecting group of patients who do not represent the larger study cohort. We have included comparative data for the broader monotherapy groups to facilitate comparisons with early dropouts and noncompleters, but we cannot assess the effect of patient dropouts. In addition, the initial starting dose of quetiapine used in the study may have been too low for some patients, which could potentially have led to early discontinuation or suboptimal outcomes. To preserve routine clinical practice, no specific scales were used to assess treatment-emergent motor dysfunction, which may have led to a less rigorous assessment, and the assessment visit interval was large, so some events may have been missed. Although patients were free to receive supporting therapies such as psychotherapy, these were not documented, so we are unable to assess their impact on outcomes. Finally, setting the threshold of statistical significance at $p < .001$ afforded us confidence that, despite multiple comparisons, the statistical differences were meaningful; however, it also means that many clinically meaningful differences cannot be described as "statistically significant." We urge readers to use their clinical judgment when critically appraising these data; all p values and estimates of precision such as confidence intervals have been presented, and we have provided NNT estimates to facilitate comparison.

As noted by the Cochrane Schizophrenia Group, most of the randomized controlled trials conducted for schizophrenia are North American; however, this region represents only 2% of the worldwide population of people with schizophrenia.[22] These naturalistic data from less-studied outpatient communities highlight the variability in clinical and functional outcomes associated with long-term antipsychotic treatment. Olanzapine monotherapy was associated with the lowest risk of all-cause discontinuation and the longest duration of treatment compared with risperidone, quetiapine, and haloperidol monotherapies. In addition, olanzapine-treated patients were more likely to respond to treatment and to do so more quickly than patients on other monotherapies. Overall, these findings are consistent with a meta-analysis which suggested that atypical antipsychotics were associated with significantly lower rates of relapse and treatment failure than conventional antipsychotics.[35] Treatment of schizophrenia requires a long-term approach that optimizes the patient's likelihood of achieving meaningful outcomes. The trade-offs between effectiveness and tolerability must be carefully evaluated when selecting an appropriate medication, because patients stay longer on treatments that offer sustained effectiveness and acceptable tolerability. Future work aims to identify potential predictors of treatment outcomes in order to assess whether modification of these risk factors can change the course of outcome for patients.

Drug names: clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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