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ORIGINAL RESEARCH

Atypical Treatment Switches in Schizophrenia Patients: Drivers and Associated Outcomes

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Objective: To describe and compare demographics and outcomes among patients with schizophrenia who have switched atypical treatments versus non-switchers.

Methods: Data were extracted from the Adelphi Schizophrenia Disease Specific Programme™ conducted from January to May 2014 in the United States. Participating physicians provided information on their next 10 consulting schizophrenia patients aged ≥ 18 years; the same patients were invited to voluntarily complete a patient self-completion form (PSC). Patients were considered switchers (S) or non-switchers (NS) based on their physician-provided treatment history. S were patients who had switched, stopped or added an atypical treatment within the last 2 years. NS had no treatment changes within the last 2 years or were receiving their first-line treatment (for ≥ 3 months). Demographics, clinical characteristics and outcomes among S and NS were compared using both descriptive and multivariate statistics.

Results: One-hundred fifty physicians provided data on 1003 patients with schizophrenia (395 S, 608 NS); 500 patients completed a PSC (170 S, 330 NS). When compared with NS, S were more likely to be unemployed (p=0.0060), have a caregiver (p<0.0001), have greater activity impairment as assessed by Work and Productivity Activity Impairment (p=0.0031), be hospitalized for schizophrenia (p<0.0001) and have had a greater mean number of hospitalizations in the last 12 months (p=0.0012). NS vs S were more likely to have much or very much improved illness (p<0.0001) and less severe disease (p<0.0001) as assessed by Clinical Global Impression.

Conclusion: Despite switching drugs, some schizophrenia patients continue to have high levels of disease burden, suggesting that currently available therapies are insufficiently effective in these patients.

Keywords: schizophrenia, atypical treatment, switching, compliance, outcomes, quality of life, EQ-5D, WPAI, CGI

Introduction

Schizophrenia is a common psychotic disorder that affects over 21 million people worldwide[1] and is one of the leading causes of disability globally.[2] The lifetime prevalence of schizophrenia is approximately 1%.[3] Despite this low prevalence, the health, social and economic burden of schizophrenia is considerable.[4] The total cost of schizophrenia in the United States (US) was approximately $156 billion in 2013;[5] approximately $38 billion was due to direct healthcare costs, of which $15 billion was due to costs resulting from inpatient care.[5–7]

Schizophrenia is a chronic disease characterized by a range of symptoms known as positive (psychotic symptoms such as delusions and hallucinations),[1] negative (such as reduced emotional expression and avolition)[1] and cognitive (such as disorganized speech, thought or attention).[8,9] Schizophrenia symptoms generally begin in late adolescence or early adulthood and the disease is often profoundly disabling without treatment.[10]

Antipsychotic agents are pharmacotherapies for the treatment of schizophrenia; these consist of first-generation (typical) and second-generation (atypical) agents. Prompt initiation of pharmacotherapy after schizophrenia diagnosis is recommended[1] and atypical antipsychotics are recommended as first-line therapies.[11]

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Antipsychotic switching is a common occurrence in schizophrenia patients. Results from clinical trials indicate that approximately one third of patients switch antipsychotics within a year of treatment initiation.[12,13] Analyses of pharmacy or prescription records revealed antipsychotic switches in 11% to 42% of patients.[14–16] The reasons for switching are diverse and may include issues with efficacy (such as persistent symptoms, relapse or insufficient functioning achieved), tolerability (such as extrapyramidal side effects, sedation, metabolic disorders or sexual dysfunction), non-compliance, or patient or family preference.[17]

Although antipsychotic switching is informed by valid concerns, switching is associated with increased risk of relapse and healthcare resource utilization. A retrospective study of Medicaid claims from six US states over a period of 6 years revealed that patients with schizophrenia, bipolar disorder or major depressive disorder who switched antipsychotics had a shorter time to disease relapse, other psychiatric relapse, emergency room visit or inpatient admission when compared to patients who did not switch.[18]

To further explore the possible associations between antipsychotic switching and outcomes, we performed an analysis of real-world survey data to describe and compare the demographics and outcomes amongst schizophrenia patients who have switched atypical treatments versus those that did not switch. As improved efficacy and tolerability are often the goals of switching, this analysis of treatment outcomes can determine if these goals were achieved in real life.

Materials and Methods

Data for this study were drawn from the Adelphi Schizophrenia Disease Specific Programme (DSP)™ conducted from January to May 2014 in the US. DSPs are large surveys conducted in clinical practice that describe current disease management, disease-burden impact and associated treatment effects (clinical and physician-perceived). The DSP is a point-in-time survey of physicians and their patients presenting in a real-world clinical setting. The DSP methodology has been described and validated previously.[19–21]

Participating Physicians and Patients

Participating physicians were hospital or office-based psychiatrists who had been practicing for 2 to 40 years at time of study, saw ≥ 6 patients with schizophrenia per week and were personally responsible for treatment decisions. Participating patients were aged ≥ 18 years, had a diagnosis of schizophrenia and were not currently participating in a clinical trial.

Data Collection

Participating physicians were instructed to complete a patient record form (PRF) for the first 10 consecutive patients who they saw in their daily clinical practice who met the eligibility criteria. PRFs contained questions related to demographics, diagnosis, management, clinical status, concomitant conditions, current treatment and treatment history.

Patients were classified as switchers (S) or non-switchers (NS) on the basis of the physician-provided treatment history. S were patients who had switched, stopped or added on an atypical treatment within the last 2 years; NS patients had no treatment changes within the last 2 years or were in receipt of their first-line treatment, which they had been receiving for at least 3 months.

Disease severity and improvement were based on physician-reported Clinical Global Impression (CGI) scale on current treatment. The CGI is a brief three-item physician-rated scale that assesses illness severity, global improvement or change, and therapeutic response.[22] Severity of illness was operationalized as mild illness if the patients were rated as "normal, not at all ill", "borderline mentally ill" or "mildly ill"; moderate illness if patients were rated as "moderately ill" or "markedly ill"; and severe illness if patients were rated as "severely ill" or "among the most extremely ill patients" on the CGI. Patients rated as "very much improved" or "much improved" were considered responders; patients rated as "minimally improved" were considered partial responders; and patients rated as "no change", "minimally worse", "much worse" or "very much worse" were considered non-responders.

Physicians assessed patient compliance with a 5-point scale. Compliance groups were derived according to the following: "always compliant" = always compliant; "sometimes compliant" or "often compliant" = sometimes compliant; and "not at all compliant" and "rarely compliant" = non-compliant.

In the analysis of drivers of switching, high-risk drugs for weight gain (at previous regimen) were olanzapine (oral/depot), chlorpromazine, iloperidone, paliperidone (oral/depot), quetiapine and risperidone.[23,24] Central nervous system (CNS) comorbidities were anxiety, depression, insomnia and stress. Cardiovascular comorbidities were hypertension, diabetes, obesity and dyslipidemia.

Each patient for whom the physician completed a PRF was then invited to complete a patient self-completion form (PSC). Upon agreement, patients provided informed consent to participate. PSCs contain questions on demographics and impact of current condition. Self-rated health was assessed by the EuroQoL 5-dimension (EQ-5D) Visual Analogue Scale (VAS) and utility score; higher scores indicate better health.[25,26] Impairment was assessed by the Work and Productivity Activity Impairment (WPAI);[27] higher scores indicate greater impairment. Overall life satisfaction was assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q);[28] higher scores indicate better quality of life. Patients were also asked to self-rate their overall satisfaction in the past week (available responses were very poor, poor, fair, good and very good). PSCs were completed by the patient independently of the physician immediately after consultation and were returned in a sealed envelope to ensure confidentiality.

Ethics

Patients completing a PSC provided informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. Physicians provided consent to participate and provide patient information during screening into the study. Data were collected such that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt. Data collection was consistent with the European Pharmaceutical Marketing Research Association guidelines[29] and as such ethics committee approval was not required. The survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996,[30] and Health Information Technology for Economic and Clinical Health Act legislation.[31]

Statistical Methods

Analyses were performed using Stata 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Descriptive statistics used were numerical (expressed as count, mean and standard deviation) or categorical (expressed as count and percentage of patients falling into each response). Bivariate statistical tests used to compare outcomes between groups included *t*-tests or analysis of variance for numerical variables, Mann–Whitney U (non-parametric) tests for ordered categorical variables, and Fisher's Exact test or chi-squared tests for non-ordered categorical variables.

Regression analyses were used to determine the effect associated with being S, after adjusting for age, gender, Body Mass Index (BMI), high risk of weight gain drugs and the presence of specified comorbid conditions. Regression type was dependent on the outcome being modeled; negative binomial being employed for count outcomes, logistic for binary outcomes and linear regression for other continuous outcomes.

Results

Physicians (n = 150) provided data on 1003 patients with schizophrenia, of which 395 were classified as S and 608 as NS. A total of 500 patients completed a PSC (170 S and 330 NS).

Patient Demographics and Reasons for Choice of Current Treatment

Mean patient age was 41.3 years and was similar between groups (S vs NS, 41.2 years vs 41.4 years; p=0.7889). Most patients were male (557/1003; 55.5%); when compared with S, a greater proportion of NS were male (56.6% vs 53.9%; p=0.4353). Mean BMI was 28.9 kg/m^2 and was similar between S (28.9 kg/m^2) and NS (28.8 kg/m^2) (p=0.8413). S were more likely to be unemployed (62.1% vs 50.5%; p=0.0060) and have a caregiver (44.8% vs 27.8%; p<0.0001) when compared with NS (Table 1).

Most physicians chose current treatment regimens considering effects on positive (S vs NS, 92.2% vs 92.4% of physicians; p=0.9036) or negative (72.7% vs 74.8%; p=0.4618) symptoms (Supplementary Table 1). When comparing

Table 1 Patient Demographics

	Overall	Switcher	Non-Switcher	*P*-value (test[a])
Age				
n	1003	395	608	
Mean (SD)	41.3 (14.6)	41.2 (15.0)	41.4 (14.3)	0.7889 (TT)
Gender				
n	1003	395	608	
Male	557 (55.5)	213 (53.9)	344 (56.6)	0.4353 (FE)
BMI, kg/m^2				
n	883	350	533	
Mean (SD)	28.9 (6.2)	28.9 (6.3)	28.8 (6.1)	0.8413 (TT)
Patient current employment				
n	995	391	604	
Full-time	115 (11.6)	44 (11.3)	71 (11.8)	0.0060 (CH)
Part-time	166 (16.7)	47 (12.0)	119 (19.7)	
Homemaker	63 (6.3)	20 (5.1)	43 (7.1)	
Student	59 (5.9)	21 (5.4)	38 (6.3)	
Retired	44 (4.4)	16 (4.1)	28 (4.6)	
Unemployed	548 (55.1)	243 (62.1)	305 (50.5)	
Caregiver				
n	926	362	564	
Yes	319 (34.4)	162 (44.8)	157 (27.8)	<0.0001 (FE)

Notes: [a]Indicates statistical test performed. All values n (%) unless otherwise indicated.
Abbreviations: BMI, body mass index; CH, chi-squared test; FE, Fisher's exact test; SD, standard deviation; TT, Student's *t*-test.

S with NS, physicians were more likely to choose current treatment regimen based on reducing aggression (33.7% vs 27.3% of physicians; p=0.0341), reduced risk of diabetes (29.9% vs 21.7%; p=0.0045), reduced risk of elevating of plasma glucose (21.0% vs 15.1%; p=0.0173), reduced risk of weight gain (26.1% vs 19.2%; p=0.0124) and value for money (24.8% vs 18.6%; p=0.0214) (Table 2 and Supplementary Table 1).

When compared with NS, S were less frequently prescribed pre-identified high-risk drugs for weight gain at current regimen, including olanzapine (13.5% vs 16.3%; p=0.2417), quetiapine (11.4% vs 15.5%; p=0.758) and risperidone (16.0% vs 21.9%; p=0.225) (Supplementary Table 2). S were more likely to be prescribed some concomitant treatments, including benzodiazepines (23.6% vs 15.6%; p=0.0021) and mood stabilizers (18.8% vs 12.0%; p=0.0034) (Supplementary Table 3).

Outcomes

When compared with NS, a greater proportion of S were hospitalized for schizophrenia (42.9% vs 16.5%; p<0.0001) and had a greater mean number of hospitalizations in the last 12 months (1.7 vs 1.3; p=0.0012). A greater proportion of NS vs S had much or very much improved illness (68.5% vs 50.5%; p<0.0001) and were considered borderline, mildly or

Table 2 Reasons for Choice of Current Regimen (All Drugs)

	Overall	Switcher	Non-Switcher	*P*-value[a]
n	1003	395	608	
Reduce aggression	299 (29.8)	133 (33.7)	166 (27.3)	0.0341
Reduced risk of inducing diabetes	250 (24.9)	118 (29.9)	132 (21.7)	0.0045
Reduced risk of elevating plasma glucose	175 (17.4)	83 (21.0)	92 (15.1)	0.0173
Reduced risk of weight gain	220 (21.9)	103 (26.1)	117 (19.2)	0.0124
Value for money	211 (21.0)	98 (24.8)	113 (18.6)	0.0214

Notes: [a]Fisher's exact test. Only significant values (P < 0.05) are shown. All values are n (%) unless otherwise indicated. See Supplementary Table 1 for complete list of reasons.

moderately ill (70.7% vs 53.2%; $p<0.0001$) as assessed by CGI. WPAI work time missed (27.5 vs 26.0; $p=0.6926$), impairment while working (27.1 vs 27.7; $p=0.8855$) and overall work impairment (42.6 vs 43.4; $p=0.8645$) were similar between S and NS. However, S vs NS reported greater mean WPAI activity impairment (51.0 vs 42.9; $p=0.0031$). EQ-5D utility score (both S and NS, 0.8; $p=0.8383$) and EQ-5D VAS (S vs NS, 64.8 vs 66.2; $p=0.4453$) were similar between groups. NS reported higher mean Q-LES-Q scores when compared with S (52.3 vs 48.7; $p=0.0608$). A greater proportion of S (24.0%) reported poor or very poor overall satisfaction in the past week than NS (15.6%) ($p=0.1674$) (Table 3).

Drivers of Switching

A logistic regression analysis was performed to identify potential drivers of treatment switching. We observed that patients were more likely to be S if they were hospitalized in the last 12 months (odds ratio [OR] 3.39, 95% confidence interval [CI] 2.29 to 5.03; $p<0.001$), prescribed a drug with high risk of weight gain (OR 3.09, 95% CI 2.21 to 4.34; $p<0.001$), had at least one other CNS comorbidity (OR 1.92, 95% CI 1.28 to 2.88; $p=0.002$), had gastroesophageal reflux disease (OR 2.80, 95% CI 1.53 to 5.12; $p=0.001$) or had severe disease (OR 3.05, 95% CI 1.56 to 5.97; $p=0.001$). Patients were less likely to be S with increasing number of comorbidities (OR 0.86, 95% CI 0.75 to 0.98; $p=0.022$) (Table 4).

Clinical and Humanistic Outcomes Associated with Switching

Multivariate regression analyses were performed to identify outcomes associated with S status. S were more likely to be unemployed (OR 1.47, 95% CI 1.05 to 2.07; $p=0.024$), have a caregiver (OR 2.03, 95% CI 1.39 to 2.97; $p<0.001$), have been hospitalized in the past 12 months (OR 3.77, 95% CI 2.53 to 5.60; $p<0.001$) and have more severe disease (coefficient 0.74, 95% CI 0.35 to 1.13; $p<0.001$). S were less likely to be always compliant with their current medication regimen (OR 0.53, 95% CI 0.37 to 0.75; $p<0.001$) or to respond to their current medication regimen (coefficient −0.57, 95% CI −0.97 to −0.17; $p=0.005$) (Table 5).

Discussion

This analysis of real-life data from schizophrenia patients and their physicians revealed that patients who switched atypical treatments in the past 2 years had significantly poorer clinical outcomes and were more likely to need caregiver support when compared with NS.

Reasons for antipsychotic switching may include poor efficacy, tolerability and compliance.[17,32–34] In this study, we observed that lower proportions of S had much or very much improved illness, were considered borderline, mildly or moderately ill, and were always compliant when compared with NS. Although improved efficacy or tolerability may have been the motivation for switching, the results from this study indicate that switching was not associated with these outcomes. Additionally, we observed that S had an increased likelihood of unemployment and need for a caregiver. Schizophrenia patients experience great social difficulties, particularly with respect to employment, and this may explain why some seek to switch treatments.[35] Caregiver support is also a concern for many patients, as social barriers and lack of family support may drive patients and their caregivers to try switching treatments.[36] Our findings suggest that there is an absence of effective atypical antipsychotics available when switching from a previous atypical antipsychotic.

The two most common reasons for choice of current treatment regimen reported by physicians were effects on positive or negative symptoms; similar proportions of physicians based their treatment decisions on these reasons for both S and NS. In contrast, we observed that significantly greater proportions of physicians based their treatment decisions around metabolic concerns (diabetes, plasma glucose or weight gain) for S than NS. These results are consistent with the known risks of weight gain with atypical antipsychotics,[23] and concerns regarding the already increased risk of metabolic syndrome and obesity in this patient population.[37,38] These results also suggest that there is an unmet need for antipsychotics that can reduce the demand for switch due to these metabolic side effects.

Although we observed poorer outcomes and compliance in S vs NS, a 2005 review of atypical antipsychotic switching studies revealed that switching was generally associated with improved outcomes.[39] For example, improved positive and negative symptom scale (PANSS) and CGI scores were observed after switching from either atypical or typical antipsychotics to quetiapine,[40] ziprasidone[41] or aripiprazole.[42] A more recent observational study on 568 patients

Table 3 Patient Clinical Characteristics and Hospitalizations

	Overall	Switcher	Non-Switcher	*P*-value (test[a])
Hospitalized for problems relating to schizophrenia				
n	985	385	600	
Yes	264 (26.8)	165 (42.9)	99 (16.5)	<0.0001 (FE)
Number of hospitalizations				
n	216	136	80	
Mean (SD)	1.6 (0.9)	1.7 (1.0)	1.3 (0.6)	0.0012 (TT)
CGI patient's improvement (physician-reported)				
n	998	394	604	
Much worse	6 (0.6)	3 (0.8)	3 (0.5)	<0.0001 (CH)
Minimally worse	14 (1.4)	5 (1.3)	9 (1.5)	
No change	42 (4.2)	17 (4.3)	25 (4.1)	
Minimally improved	309 (31.0)	162 (41.1)	147 (24.3)	
Much improved	545 (54.6)	183 (46.4)	362 (59.9)	
Very much improved	68 (6.8)	16 (4.1)	52 (8.6)	
Unknown	14 (1.4)	8 (2.0)	6 (1.0)	
CGI illness severity				
n	996	392	604	
Normal, not at all ill	12 (1.2)	3 (0.8)	9 (1.5)	<0.0001 (CH)
Borderline mentally ill	48 (4.8)	14 (3.6)	34 (5.6)	
Mildly ill	177 (17.8)	51 (13.0)	126 (20.9)	
Moderately ill	410 (41.2)	143 (36.5)	267 (44.2)	
Markedly ill	227 (22.8)	109 (27.8)	118 (19.5)	
Severely ill	107 (10.7)	64 (16.3)	43 (7.1)	
Among the most extremely ill patients	15 (1.5)	8 (2.0)	7 (1.2)	
WPAI				
n	133	37	96	
Percent work time missed, mean (SD)	26.5 (19.7)	27.5 (22.3)	26.0 (18.7)	0.6926 (TT)
n	125	34	91	
Percent impairment while working, mean (SD)	27.5 (21.8)	27.1 (19.8)	27.7 (22.6)	0.8855 (TT)
n	125	34	91	
Percent overall work impairment, mean (SD)	43.1 (22.9)	42.6 (22.4)	43.3 (23.2)	0.8645 (TT)
n	456	147	309	
Percent activity impairment, mean (SD)	45.5 (27.2)	51.0 (28.3)	42.9 (26.4)	0.0031 (TT)
EQ-5D				
n	409	135	274	
Mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8383 (TT)
EQ-5D VAS				
n	392	129	263	
Mean (SD)	65.8 (17.8)	64.8 (19.2)	66.2 (17.0)	0.4453 (TT)
Q-LES-Q				
n	360	118	242	
Mean (SD)	51.2 (17.1)	48.7 (17.3)	52.3 (17.0)	0.0608 (TT)
Patient-reported overall satisfaction in past week				
n	393	125	268	
Very poor	13 (3.3)	7 (5.6)	6 (2.2)	0.1674 (CH)
Poor	59 (15.0)	23 (18.4)	36 (13.4)	
Fair	187 (47.6)	59 (47.2)	128 (47.8)	
Good	122 (31.0)	34 (27.2)	88 (32.8)	
Very good	12 (3.1)	2 (1.6)	10 (3.7)	

Notes: [a]Indicates statistical test performed. All values n (%) unless otherwise indicated.

Abbreviations: CGI, Clinical Global Impression; CH, chi-squared test; FE, Fisher's exact test; EQ-5D, EuroQol 5-dimension 3-level; Q-LES-Q, Quality of Life, Enjoyment, and Satisfaction Questionnaire; SD, standard deviation; TT, Student's *t*-test; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.

Table 4 Drivers of Switching

	Odds Ratio (95% CI)	*P*-value
Age	0.991 (0.978 to 1.003)	0.145
Gender		
Male	1 (base)	
Female	1.217 (0.923 to 1.606)	0.164
BMI	1.000 (0.973 to 1.025)	0.915
Number of comorbidities	0.857 (0.750 to 0.978)	
Hospitalizations[a]		
Not hospitalized	1 (base)	
Hospitalized	3.392 (2.287 to 5.031)	<0.001
Drug with risk of weight gain[b]		
Not high-risk drug	1 (base)	
High-risk drug	3.093 (2.206 to 4.337)	<0.001
CNS comorbidities[c]		
None	1 (base)	
At least 1 CNS comorbidity	1.919 (1.281 to 2.876)	0.002
CV comorbidities[d]		
None	1 (base)	
At least 1 CV comorbidity	1.572 (0.989 to 2.498)	0.056
GERD		
No GERD	1 (base)	
GERD	2.803 (1.535 to 5.118)	0.001
CGI overall impression of illness severity		
Mild	1 (base)	
Moderate	1.394 (0.898 to 2.165)	0.139
Severe	3.050 (1.559 to 5.967)	0.001

Notes: Results were based on 849 observations. Odds ratios are based on the patient being a switcher. [a]Whether patient was hospitalized in last 12 months. [b]High-risk drugs were olanzapine (oral/depot), chlorpromazine, iloperidone, paliperidone (oral/depot), quetiapine and risperidone (oral/depot). [c]Central nervous system comorbidities were anxiety, depression, insomnia or stress. [d]Cardiovascular comorbidities were hypertension, diabetes, obesity or dyslipidemia.

Abbreviations: BMI, body mass index; CGI, clinical global impression; CI, confidence interval; CNS, central nervous system; CV, cardiovascular; GERD, gastroesophageal reflux disease.

Table 5 Multivariate Regression Analyses

	n[a]	Value[b] (95% CI)	*P*-value
Unemployed	872	1.474 (1.051 to 2.068)	0.024
Has caregiver	818	2.033 (1.390 to 2.974)	<0.001
Has professional caregiver	272	1.388 (0.808 to 2.382)	0.235
Always compliant	862	0.526 (0.370 to 0.748)	<0.001
Hospitalization[c]	856	3.768 (2.534 to 5.604)	<0.001
Disease severity	873	0.741[d] (0.355 to 1.126)	<0.001
Responding to treatment	862	−0.569[d] (−0.969 to −0.169)	0.005
WPAI activity impairment	403	6.547[d] (−0.820 to 13.914)	0.081
EQ-5D VAS	345	1.547[d] (−3.269 to 6.363)	0.525

Notes: Results are based on the patient being a switcher. [a]Number of observations. [b]All values are odds ratios unless otherwise indicated. [c]Hospitalization in the past 12 months. [d]Coefficient (β); linear regression.

Abbreviations: CI, confidence interval; EQ-5D, EuroQol 5-dimension; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.

revealed that treatment switch between atypical antipsychotics was associated with significant decreases in PANSS and CGI scores, and improved compliance.[34] In contrast, switching from an atypical antipsychotic or haloperidol to olanzapine was not associated with improvements in PANSS scores.[43] An analysis of data from the Clinical

Antipsychotic Trials of Intervention Effectiveness (CATIE) trial revealed that there were no significant differences in outcomes such as symptoms, neurocognition, quality of life, neurological side effects, weight and health costs between patients who stayed on the same atypical antipsychotic after randomization and those who switched to a different atypical antipsychotic.[44] Patients who switched antipsychotics (both typical and atypical) were significantly more likely to be hospitalized when compared to those who did not switch.[45,46] However, it is important to note that these studies are not directly comparable to each other or to the present study due to differences in methodology and patient populations.

Logistic regression analyses revealed several drivers associated with S status. The drivers associated with the greatest risk for switching (high-risk drug of weight gain, hospitalizations or severe disease) in this study are consistent with previous observations.[23] A prospective observational study in real-life clinical practice revealed that patients that switched from an atypical antipsychotic were more likely to do so because of weight gain when compared with those who switched from a typical antipsychotic.[47] Patients who are hospitalized or experience persistent severe disease despite medication compliance would be candidates for antipsychotic switching, consistent with the results observed here.

It is important to note that there may be a bidirectional association between these drivers and switching. For example, a patient prescribed a drug of high weight gain risk is more likely to be a S. However, it is not clear if the patient was switched due to weight gain or other concerns surrounding a high-risk drug or if the patient was switched to a high-risk drug because they had not responded to other drugs with a lower risk of weight gain. This bidirectional relationship may be applicable to other variables examined in this study.

Although S had an increased likelihood of unemployment, hospitalization, need for caregiver, more severe disease, and poorer compliance and response, additional factors beyond treatment choice and treatment decisions may also impact these outcomes. Such factors may include demographic and clinical characteristics not captured in this survey, patient-physician relationships, support network available to the patient, and social and cultural circumstances unique to the patient. Additionally, the health insurance status of patients is variable and may affect the accessibility and quality of treatment received.[48]

The poorer outcomes observed in S vs NS may suggest that despite the advantages of currently available atypical antipsychotics, these therapies continue to have important shortcomings regarding efficacy and metabolic side effects. Patients treated with atypical antipsychotics may continue to experience negative and positive symptoms. Side effects associated with atypical antipsychotics may contribute significantly to cardiometabolic and endocrine side effects.[49] The greater disease severity and reduced improvement observed in S vs NS, along with metabolic comorbidities acting as a driver for switching, are consistent with the shortcomings of atypical antipsychotics.

There have been reports of reduced side effects and improved function among patients switching from atypical antipsychotic polypharmacy to monopharmacy.[50,51] Additionally, there is some evidence that antipsychotic dose reduction may also help to reduce side effects while maintaining efficacy.[52] If considered in future, these alternatives may help to offset the potential problems associated with switching one atypical antipsychotic drug for another.

This study had some limitations. The data obtained from the DSP were not based on a true random sample of physicians or patients. Physician participation was influenced by willingness to complete the survey. Although no formal patient selection procedures were used, physicians were asked to provide information on the next 10 patients they consulted. While the point-in-time study design prevented any conclusions about causal relationships, identification of significant associations was possible. However, it was not possible to define precise temporal relationships between switching and outcomes. For example, data on response and compliance were based on physician assessment at time of survey, while switching may have occurred at any time in the previous two years. It is possible that patients who switched recently before the time of survey may not yet have achieved the full efficacy of their new regimen. While recall bias may have affected patient and physician responses to the questionnaires, this is a common limitation of surveys. However, data were collected at the time of each patient's consultation and physicians had access to the patient's medical history; these were both expected to have reduced the likelihood of recall bias. Although a total of 1003 PRFs were completed, only 500 patients completed PSCs. It is unclear if this introduced bias into the results.

Conclusions

Patients with schizophrenia who switched atypical antipsychotic treatments experienced worse clinical and social outcomes than those who did not. While there are a variety of factors that may drive patients or their physicians to seek a switch, we found that switching treatments does not achieve improved results for these patients. The poorer outcomes and increased need for caregiver support in S vs NS suggest that more efficacious therapies are needed to avoid switches and also to provide an effective treatment option when a switch is warranted in patients with schizophrenia.

Data Sharing Statement

All data that support the findings of this study are intellectual property of Adelphi Real World. All requests should be addressed directly to Jason Shepherd at jason.shepherd@adelphigroup.com.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

RK, ZQ and FC are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA who may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. The authors report no other conflicts of interest in this work.

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