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Reasons for Antipsychotic Treatment Switch:
A Systematic Retrospective Review of Prescription Records and Prescriber Notes

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ABSTRACT

Objective: Switching of antipsychotic medications, which are used for many psychiatric conditions, is common. However, reasons and clinical documentation of such switches have scarcely been studied.

Methods: A systematic, retrospective review of prescription records and prescriber notes was conducted to characterize reasons for and types of antipsychotic switches at one hospital during inpatient or outpatient care, starting August 1, 2017, until 270 antipsychotic switches with type and reasons were collected, as required by power analysis.

Results: After removing 7 cases in which quetiapine was switched to a non-antipsychotic agent, 263 antipsychotic switches involving 195 unique subjects (median age = 31 [interquartile range, 24–47] years; schizophrenia = 36.9%, bipolar disorder = 27.7%, schizoaffective disorder = 18.5%) were analyzed. Frequent reasons for antipsychotic switch were intolerability (45.7%) and inefficacy/clinical worsening (17.6%). Reasons did not differ by race ($P = .2644$), age ($P = .0621$), or insurance type ($P = .2970$), but differed heterogeneously regarding different reasons by sex ($P = .004$). The most common reported switches were from second-generation oral antipsychotics (SGA-OAPs) to other SGA-OAPs (N = 155, 58.9%), mostly due to tolerability or inefficacy; second-generation long-acting injectable antipsychotics (SGA-LAIs) to SGA-OAPs (11%), mostly due to intolerability, patient preference, or insurance coverage problems; and SGA-OAPs to SGA-LAIs (10.7%) due to nonadherence. Reasons for antipsychotic switch were properly documented in 208 (79.1%) of the prescriber notes.

Conclusions: In this retrospective chart review, switching varied by sex regarding reasons and occurred almost in half of the cases due to intolerability. Different reasons predominated in switches from SGA-OAP to SGA-OAP, SGA-LAI to SGA-OAP, and SGA-OAP to SGA-LAI. One in 5 switches were not properly documented, requiring attention.

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Antipsychotics are an essential component of acute treatment and relapse prevention in psychotic disorders.[1–4] They are often classified as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).[5] Both types of antipsychotics work by blocking the dopamine D_2 receptors in the brain; however, SGAs also act on the serotonin receptor, especially 5-HT_2 and 5-HT_{1c} as well as muscarinic receptors.[5–9]

Despite their efficacy, antipsychotics may cause a variety of undesirable side effects including motor symptoms such as Parkinsonism, akathisia, tardive dyskinesia, metabolic symptoms like weight gain or dyslipidemia (which may lead to cardiovascular complications), endocrine symptoms such as elevated prolactin, and other symptoms such as sleep disturbance and nausea/vomiting.[10–13] These unfavorable side effects have been reported as reasons for nonadherence and subsequent unfavorable outcomes.[14,15]

Often, side effects create a dilemma for prescribers as to whether a patient should be switched and, if so, to which medication[16] and in which ways.[9,17–21] Such difficult clinical decisions are crucial when trying to balance efficacy and tolerability, treatment continuation, adherence, and overall outcomes. A recent retrospective study analyzing insurance database claims[22] found that switching is associated with an increased risk of relapse in schizophrenia, bipolar disorder, and major depressive disorder, yet reasons for antipsychotic switches were not documented. Therefore, results could have been confounded by indication, leading to reverse causation, in that more-severely ill or worsening patients required more antipsychotic switches.

According to a retrospective follow-up study[23] done in 522 newly admitted patients who started with an oral antipsychotic, patients taking SGAs in comparison to FGAs had a lower incidence of switching to another antipsychotic medication (adjusted OR = 1.79; 95% CI = 1.15–2.78), and

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Clinical Points

- Specific reasons for antipsychotic switches and quality of prescriber notes have been infrequently studied. A systematic retrospective chart review was conducted.
- Side effects were frequently reported as reasons for medication switch, which differed regarding specific reasons by sex in various ways, followed by inefficacy, patient preference, insurance problems, and poor adherence. Notably, 21% of medication switches were inadequately documented.

patients on FGAs switched earlier than patients on SGAs (median time interval of 24 days with FGAs vs 170 days with SGAs).[23] However, specific reasons for such antipsychotic switches were not reported.

Risk factors for antipsychotic switches have been frequently studied and include preexisting and worsening depression or akathisia, particularly in the early stages of treatment; female sex; older age; and type of antipsychotic.[24,25] In contrast, specific reasons for antipsychotic switches have been less frequently studied and include inefficacy or symptomatic worsening, side effects and lack of tolerability, adherence problems, and patient preference.[25–28] However, research in this area has not been recently updated, despite the introduction of better tolerated antipsychotic drugs and the widespread adoption of newer formulations of long-acting injectable antipsychotics, whose indications and use are expanding beyond schizophrenia.[29–31]

Based on the above, we aimed to conduct a systematic retrospective review of prescription records and prescriber notes to characterize reasons for and type of antipsychotic medication switches in a large, academic psychiatric hospital and outpatient clinic in the borough of Queens, New York City.

METHODS

Data Selection

We conducted a computerized search of The Zucker Hillside Hospital's Chart Viewing Module (CVM)'s medical notes starting August 1, 2017, and continuing to collect consecutive antipsychotic switches until 270 cases with information on type and reason of the antipsychotic switch as indicated by the power analysis (see below). An antipsychotic switch was defined as a change in antipsychotic medication that was either reported in the notes by the physicians or observed in the prescription log.

Subjects

Included in the review were patients treated in the inpatient and outpatient services at the Zucker Hillside Hospital, New York, without age or diagnostic restriction, for whom an antipsychotic switch had been electronically identified and then confirmed by an individual chart review performed by at least 2 independent investigators. The study was reviewed and deemed exempt from requiring patient consent by the local institutional review board (IRB#18–0654).

Outcomes and Data Collection

Primary and secondary outcomes were prespecified. Primary outcomes included type of medication switch and reasons for medication switch. Secondary outcomes included the evaluation of proper documentation of such switches. Thus, after identification of medication switches, 3 investigators (N.T., K.V., and Y.S.) independently extracted data from the patient's chart, including demographic information, *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) diagnosis, comorbid psychiatric/medical illnesses, antipsychotic medication(s) pre- and post-switch, cotreatments, and duration of the antipsychotic medication before switch. Reasons for every switch were collected and coded. Additionally, prescriber's notes were categorized into complete (ie, prescribers reported the reason for the switch); incomplete (ie, prescribers mentioned the switch being made, but did not report the reason for that switch); and absent (ie, no mention of the switch identified by prescription record review at all and no mention of the reason why the switch was made). Inconsistencies were resolved by consensus or involvement of a fourth investigator (D.G.).

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the collected data. Normality of continuous variables was tested using Shapiro-Wilk *W* tests. Associations between variables were tested using univariate analyses. Univariate χ^2 tests were used to explore associations between categorical variables. *T* tests were used for normally distributed continuous variables, and Wilcoxon/Kruskal-Wallis tests were used for non-normally distributed continuous variables, reported as χ^2 values. A power analysis indicated that 270 switches would comprise a sufficient sample to achieve more than 90% power for a χ^2 test of independence up until df = 15 to detect a medium effect size ($\varphi = 0.3$).[32] Therefore, data collection was stopped when 270 consecutive switches had been collected. Statistical significance was set at $P < .05$, uncontrolled for multiplicity. All analyses were conducted using JMP, Version *13*, SAS Institute Inc., 1989–2019.

RESULTS

Population

The initial study sample included 270 consecutive individual antipsychotic switches. However, 7 switches consisted of replacing low dose quetiapine for non–US Food and Drug Administration (FDA)-approved indications by other non-antipsychotic drugs, such as trazodone, mirtazapine, gabapentin, benzodiazepines, and antihistamines, and were therefore excluded from these analyses. This resulted in a total of 263 individual consecutive switches (yielding 90% power for the planned

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Table 1. Sociodemographic Characteristics of the Antipsychotic Switch Patient Sample[a]

Variable	Total (n = 195, 100%)	Female (n = 97, 49.7%)	Male (n = 98, 50.3%)	*P* value[b]
Age, y, median (Q1, Q3)	31 (24, 47)	36 (25.5, 55.5)	27.5 (24, 40.25)	.0107
Race				.9161
White	92 (48.2)	48 (50.0)	44 (46.3)	
Black/African American	64 (33.5)	31 (32.3)	33 (34.7)	
Asian	18 (9.4)	8 (8.3)	10 (10.5)	
Mixed/other	17 (8.9)	9 (9.4	8 (8.5)	
Primary diagnosis				.0010
Schizophrenia and related disorders	72 (36.9)	23 (23.7)	49 (50.0)	
Bipolar disorder	54 (27.7)	35 (36.1)	19 (19.4)	
Schizoaffective disorder	36 (18.5)	21 (21.7)	15 (15.3)	
Major depressive disorder	17 (8.7)	11 (11.3)	6 (6.1)	
Alzheimer's disease/dementia	6 (3.1)	4 (4.1)	2 (2.0)	
Autism spectrum disorder	5 (2.6)	0 (0)	5 (5.1)	
Personality/substance use disorder	5 (2.6)	3 (3.1)	2 (2.1)	
Marital status				.0013
Single	142 (72.8)	59 (60.8)	83 (84.7)	
Married	33 (16.9)	25 (25.8)	8 (8.2)	
Divorced/separated	11 (5.6)	8 (8.3)	3 (3.1)	
Widowed	5 (2.6)	4 (4.1)	1 (1.0)	
Unknown/unreported	4 (2.1)	1 (1.0)	3 (3.1)	
Living status				.3938
With family	165 (84.6)	78 (80.4)	87 (88.8)	
Alone	18 (9.2)	12 (12.4)	6 (6.1)	
Group home	4 (2.1)	2 (2.1)	2 (2.0)	
Unknown/unreported	8 (4.1)	5 (5.2)	3 (3.1)	
Employment status				.1984
Unemployed	105 (53.8)	44 (45.4)	61 (62.2)	
Employed	40 (20.5)	23 (23.7)	17 (17.4)	
Retired	17 (8.7)	11 (11.3)	6 (6.1)	
Disabled	13 (6.7)	8 (8.3)	5 (5.1)	
Unknown/unreported	20 (10.3)	11 (11.3)	9 (9.2)	
Insurance type				.6954
Medicaid/Medicare	104 (67.1)	34 (65.4)	42 (68.9)	
Private	51 (32.9)	18 (34.6)	19 (31.1)	

[a]Values expressed as n (%) unless otherwise noted.
[b]Reported *P* values refer to the result of χ^2 or nonparametric Wilcoxon tests comparing the two groups.
Abbreviations: Q1 = first quartile, Q3 = third quartile.

analyses), pertaining to 195 different subjects, as for some subjects more than 1 antipsychotic switch was recorded.

The subjects' median age was 31 years (interquartile range [IQR], 24–47); they were balanced on sex (male n = 98, 50.3%) and white vs non-white race (white n = 92, 48.2%) and were mostly single (n = 142, 72.8%). The most common primary diagnosis was schizophrenia and related disorders (n = 72, 36.9%), followed by bipolar disorder (n = 54, 27.7%) and schizoaffective disorder (N = 36, 18.5%). Sociodemographic data of the patient sample are detailed in Table 1. Briefly, female subjects were slightly older (median age = 36 years vs male = 27.5), more likely to suffer from bipolar disorder (36.1% vs male = 19.4%), and more frequently married (25.8% vs male = 8.2%). There were no statistically significant differences in age ($P = .7809$), sex ($P = .0738$), race ($P = .7172$), diagnosis ($P = .1882$), insurance type ($P = .5875$), employment ($P = .9328$), living ($P = .5290$), or marital ($P = .8312$) status between patients undergoing 1 medication switch vs more than 1.

Reasons for Antipsychotic Switching

Reasons for antipsychotic switch were properly documented in N = 208 (79.1%) of the prescriber notes in the electronic medical record, whereas N = 55 (20.9%) had incomplete or absent information. The median duration of antipsychotic treatment before the switch was 4.0 (IQR = 1.2–13.0) months. The most frequently reported reason for antipsychotic switching was side effects (N = 96, 45.7%), followed by lack of efficacy/clinical worsening (N = 37, 17.6%), patient preference/request (N = 29, 13.8%), insurance requirement problems (N = 22, 10.5%), poor adherence (N = 18, 8.6%), and other reasons (N = 8, 3.8%) (Figure 1). Among reported side effects (N = 96), hyperprolactinemia (N = 18, 18.8%), increased appetite/weight gain (N = 16, 16.7%), and extrapyramidal symptoms (N = 12, 12.5%) were the most frequently reported. Detailed distribution of reported side effects can be found in Figure 1.

Patient Correlates of Antipsychotic Switching

Reasons for antipsychotic switching did not differ by race ($\chi^2_{15,\ 207} = 17.9$, $P = .2644$), age ($\chi^2_{5,\ 210} = 10.5$, $P = .0621$), diagnosis ($\chi^2_{30,\ 210} = 20.3$, $P = .2526$), or type of insurance ($\chi^2_{5,\ 119} = 6.1$, $P = .2970$), but differed by sex ($\chi^2_{5,\ 210} = 22.7$, $P = .004$). Female subjects were more likely to experience antipsychotic switch due to lack of efficacy (59.5% vs male 40.5%) and side effects (58.3% vs male 41.7%), whereas men were more likely to undergo antipsychotic switch because of poor adherence (83.3% vs female 16.7%), patient preference/

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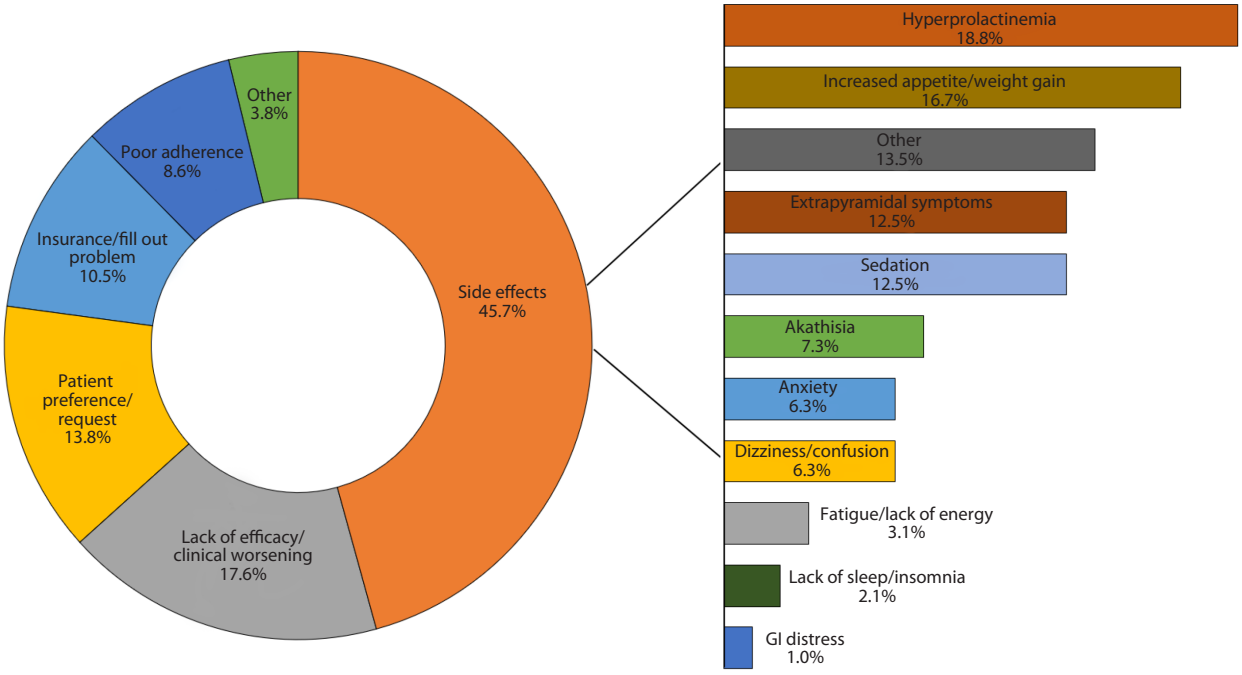
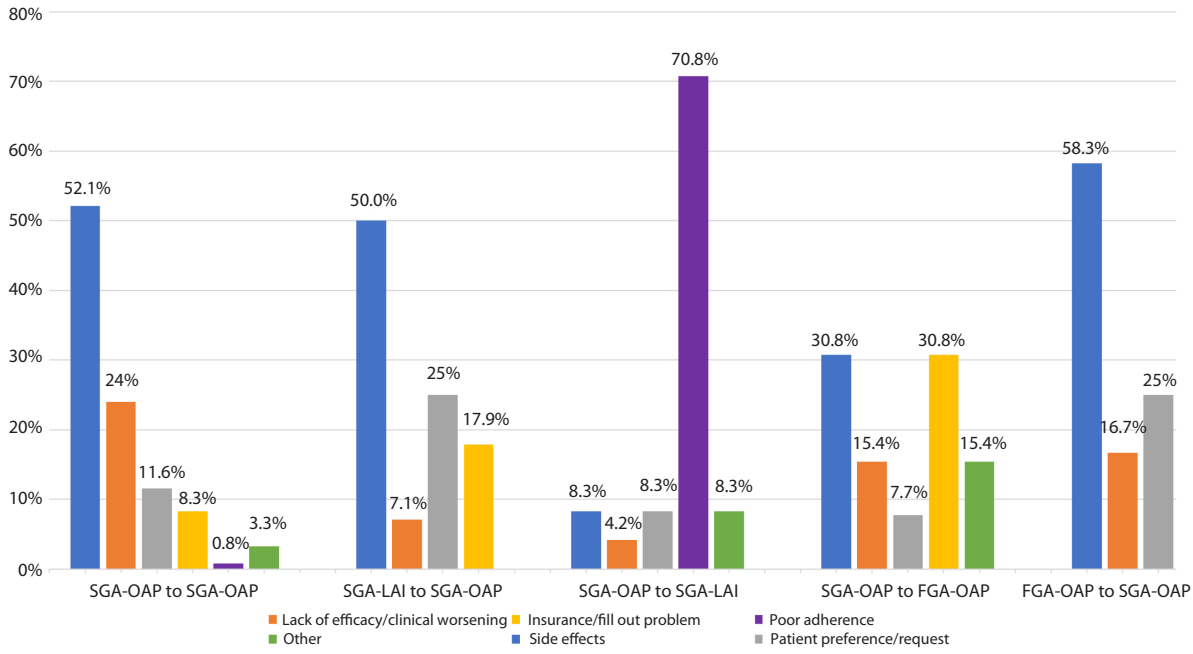
Figure 1. Distribution of Reasons for Antipsychotic Switch



Abbreviation: GI = gastrointestinal.

Figure 2. Details of Reasons for Antipsychotic Switch by Switch Combination



Abbreviations: FGA-OAP = first-generation oral antipsychotic, SGA-LAI = second-generation long-acting injectable antipsychotic, SGA-OAP = second-generation oral antipsychotic.

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request (69.0% vs female 31.0%), and insurance requirement problems (77.3% vs female 22.7%). While reasons for antipsychotic switch did not differ statistically by setting ($\chi^2_{5,\ 210} = 10.4$, $P = .0637$), inpatient compared to outpatient switches qualitatively tended to be more frequently related to lack of efficacy (33.3% vs 15.9% outpatient) or poor adherence (19.1% vs 7.4% outpatient) and less frequently related to patient preference/request (4.7% vs 14.8% outpatient).

Antipsychotic Switch Sequences and Reasons by Antipsychotic Formulation

The most frequent antipsychotic switch sequence was second-generation oral antipsychotic (SGA-OAP) to SGA-OAP (N = 155, 58.9%), followed by second-generation long-acting injectable antipsychotic (SGA-LAI) to SGA-OAP (N = 29, 11.0%) and SGA-OAP to SGA-LAI (N = 28, 10.7%). The most frequent reason for switch from SGA-OAP to SGA-OAP was side effects (n = 63, 52.1%), followed by lack of efficacy (n = 29, 24.0%). The most frequent reason for switch from SGA-LAI to SGA-OAP was side effects (n = 14, 50.0%), followed by patient preference/request (n = 7, 25.0%) and insurance requirement/authorization problems (n = 5, 17.9%). The most frequently reported reason for medication switch from SGA-OAP to SGA-LAI was poor adherence (n = 17, 70.8%). Reasons for medication switch by switch sequence are detailed in Figure 2. In the case of side effects, by individual drug, switches from risperidone to aripiprazole were the most frequently reported in the case of hyperprolactinemia (N = 6, 33.3%), aripiprazole to ziprasidone switches were the most frequently reported in cases of weight gain (N = 4, 25.0%), and quetiapine to aripiprazole switches were the most frequently reported in cases of sedation (n = 5, 41.7%).

DISCUSSION

In this systematic retrospective chart review of 263 consecutive switches in 195 individual patients, the most frequently reported switch sequence was SGA-OAP to SGA-OAP, and the most frequent reason for that switch was the presence of side effects. Among reported side effects, hyperprolactinemia (18.8%) and extrapyramidal symptoms (EPS) (12.5%) were the most frequent. While the efficacy of antipsychotics in general is thought to be at least in part mediated by dopamine D_2 receptor antagonism/partial agonism, unintended antipsychotic-related alterations in dopaminergic pathways related to motor function and prolactin secretion can lead to EPS and hyperprolactinemia. Hyperprolactinemia is difficult to manage, frequently requiring polytherapy or switching to prolactin-sparing antipsychotics,[33] and its clinical manifestations, which can include galactorrhea, sexual dysfunction, and gynecomastia, can generate significant distress and reduce quality of life.[34] EPS can be serious and stigmatizing, remaining a frequent reason for antipsychotic switch or nonadherence. However, EPS can perhaps be more easily managed than hyperprolactinemia with additional pharmacotherapy or antipsychotic dose reduction. Despite the lower incidence and severity of EPS with second-generation antipsychotics compared to first-generation antipsychotics, EPS still occur with second-generation antipsychotics, albeit with relevant between-drug differences,[11] and must be carefully considered upon selection of antipsychotic treatment.[35]

Another frequently reported side effect was increased appetite/weight gain (16.7%), which is another common reason for nonadherence and subsequent antipsychotic switch[36] and a side effect with potential long-term implications in mortality and morbidity due to its frequent clustering with metabolic syndrome and cardiovascular disease.[37–39] Due to their diverse receptor binding profiles, even within the same class, antipsychotics vary significantly in terms of their side effects profile,[9–11,40] which together with patient preferences must be considered by prescribers in order to minimize the need for preventable side effect related switches.

In this study, the 2 most frequent switches were risperidone to aripiprazole and quetiapine to aripiprazole. Aripiprazole is a partial dopamine D_2 and D_3 receptor agonist and serotonin at 5-HT_{2A} receptor antagonist,[41] a combination that allows similar symptom reduction properties yet with a somewhat better tolerability profile, particularly for metabolic and endocrine side effects, yet less favorable for akathisia, compared with other second-generation D_2 antagonists.[42,43] Other more recently approved antipsychotics, such as brexpiprazole and cariprazine also show a similar tolerability profile, albeit brexpiprazole was started less frequently than aripiprazole, and no patient was switched to cariprazine, probably attributable to the fact that these treatments had just been very recently approved by the FDA at the time of this study.

Reasons for antipsychotic switching did not differ by race, age, diagnosis, or type of insurance, but differed by sex. Interestingly, female subjects were more likely to undergo antipsychotic switch due to inefficacy (59.5% vs male 40.5%) and side effects (58.3% vs male 41.7%). This finding could be explained by previously reported differential pharmacodynamic and pharmacokinetic characteristics between males and females, whereby females reach generally higher blood antipsychotic levels than males at similar doses,[44–46] which could explain the higher frequency of intolerability-related switches but would argue against more inefficacy related switches. Our results are consistent with a recent study showing that 2 times more females described antipsychotic side effects as being severe than did males.[47] A recent retrospective study assessing patients' electronic medical records via text-mining also reported differential side effect profiles between males and females, whereby male subjects reported sexual dysfunction more frequently, while female subjects reported gastrointestinal symptoms, suicidal and self-injurious behavior, and hyperprolactinemia-related events more frequently.[48] Our findings suggesting that female subjects were more likely to undergo antipsychotic switch due to inefficacy (59.5% vs male 40.5%) are

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difficult to reconcile with the above and could relate to possible underdosing in females or a higher rate of covert (undisclosed) nonadherence in a subgroup of females in our sample. Beyond biological differences, socially acceptable/expected sex-/gender-associated roles and behaviors, such as lifestyle, diet, exercise, drug use, willingness to report side effects to their prescriber (eg, sexual dysfunction), and variable adherence to treatment may also underlie such differences. In fact, in our study, male patients were more likely to undergo antipsychotic switch because of poor adherence (83.3% vs female 16.7%) and patient preference/request (69.0% vs female 31.0%), which could be related to some of these aforementioned nonbiological factors. Albeit not significantly different, inpatient compared to outpatient switches qualitatively tended to be more frequently related to lack of efficacy and less frequently related to patient preference/request, as patients in the inpatient unit are generally more severely ill.

Surprisingly, only 5 prescriptions of clozapine were started, whereas 4 were discontinued, leading to a net gain of 1 clozapine prescription in the evaluated sample. Clozapine is the most effective and the only approved medication for treatment resistant schizophrenia.[49–54] Clinicians know this, yet clozapine remains underutilized.[55,56] Barriers to clozapine use seem to point toward lack of personal prescribing experience and concerns related to the need of blood monitoring and fear of side effects, but further efforts are clearly needed to align clozapine prescriptions to treatment resistance rates.[57,58]

In this study, the most frequently reported reason for medication switch from SGA-OAP to SGA-LAI was poor adherence. This finding is not entirely surprising, as LAIs are a safe[59–63] treatment alternative to address nonadherence and to reduce the burden associated with daily medication intake.[64–67] However, numbers appear to be very similar to those reported in SGA-LAI to SGA-OAP switches, unveiling an apparent lack of net gain in LAI prescriptions in our study sample. A wide array of surveys and focus groups have been conducted to study barriers related to LAI utilization, which include clinicians limiting their discussions on LAI formulations only to patients with demonstrated nonadherence and/or repeated hospitalizations, concerns about the possible effects of LAI formulations, and assumptions that patients will refuse LAI administration.[68–70] Given high rates of nonadherence in people with mental illness, several advantages of LAIs over oral antipsychotics,[31,61] and the fact that 36.9% of reviewed patients were diagnosed with schizophrenia, 27.7% with bipolar disorder, and 18.5% with schizoaffective disorder, each of which are conditions for which SGA-LAIs are licensed, we would have expected more frequent switches to LAIs.

In an academic center with teaching and educational programs, 21% of the medication switches assessed were not properly documented by prescribers because notes were either incomplete (ie, the switch was mentioned, but the reason for that switch was not) or absent (ie, no mention of the switch at all). It might be that these numbers could be worse in other settings, but this finding is disappointing. Formal training could help mitigate suboptimal medical notes, but other elements, such as patient overload, growing external and administrative pressures, or physician burnout, could affect the adequate recording of patient-physician communication.[71]

Limitations

First, this systematic and retrospective chart review included only a limited number of subjects. Longer and prospective observation periods may allow a more detailed characterization of antipsychotic switching trends. Nonetheless, the study was adequately powered to detect significant differences in predefined outcomes variables. Second, we studied all documented antipsychotic switches per included patient, and switch reasons may not be independent from each other within one patient. Nevertheless, we aimed to capture the treatment trajectory of all included patients, and selecting only the first antipsychotic switch type and reason could also have led to a bias. Nonetheless, we conducted additional sensitivity analyses comparing patients undergoing 1 medication switch vs more than 1 and found no statistically significant differences, minimizing risk of biased conclusions. Third, we only studied the nature of and reasons for antipsychotic switching, but outcomes of these different switches would also be of interest. This evaluation should be added in future studies. Fourth, this was a single-site naturalistic study. Although the subjects included were both in- and outpatients, replication in different settings, including non-academic hospitals or clinics and community mental health centers, is necessary. Despite these limitations, this is one of the few naturalistic studies investigating the characteristics and antipsychotic formulation sequence of, as well as the reasons for and adequate documentation of, antipsychotic switching.

CONCLUSION

In this systematic retrospective chart review study, the most frequently reported switches were from SGA-OAP to SGA-OAP due to side effects or lack of efficacy, followed by SGA-LAI to SGA-OAP due to side effects, patient preference, or insurance coverage problems, and SGA-OAP to SGA-LAI due to poor adherence. As many as 21% of the medication switches assessed were not properly documented, which merits attention.

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