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Clinical determinants, patterns and outcomes of antipsychotic medication prescribing in the treatment of schizophrenia and schizoaffective disorder: A naturalistic cohort study

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ABSTRACT

Background: Schizophrenia affects individuals, families, and systems, with treatment primarily being antipsychotic medications. Long-acting injectable (LAI) antipsychotics are increasingly being used. This study sought to identify predictors of antipsychotic choice, in terms of formulation (LAI vs oral) and class (FGA vs SGA), and clinical outcomes.

Methods: 123 patients who received LAI antipsychotics were diagnosis-matched to patients who received oral antipsychotics. Sociodemographic and clinical factors were extracted from the medical record, including indicators of illness severity. Groups were compared with Chi-Square and t-tests, and logistic regression models were used to identify independent predictors of antipsychotic choice.

Results: Patients that received LAIs had longer admissions, more complex discharges, and greater illness severity; however, there were no differences in readmission rates. Independent predictors of LAIs included younger age, being single, and longer admission. Patients who received FGA LAIs were more likely to use substances and be undomiciled compared to SGA LAIs, with the only predictor being older age. Oral FGAs were more likely than Oral SGAs to be prescribed to older and female patients, as well as those with co-occurring substance use, complex discharges, and longer admissions.

Conclusions: Illness severity and duration of illness appear to drive choice of LAI vs. oral antipsychotic medication and FGA vs. SGA. While LAIs were prescribed to patients with greater illness severity, readmission rates were equivalent to those receiving oral medication, supporting the use of LAI in patients with greater illness severity. Rationales for prescribing LAIs to younger patients and FGAs to older patients are discussed.

1. Introduction

Schizophrenia is a chronic, progressive mental disorder that affects 1% of the general population and has profound effects on individuals, families, and communities (Diatta et al., 2007). The mainstay of schizophrenia treatment is antipsychotic medication; however, the usefulness of these medications may be hampered by adverse effects, and poor adherence.

The first approved antipsychotic medication (AP) was Chlorpromazine (brand name Thorazine) in 1951 (Table 1). Chlorpromazine, as well as other first-generation antipsychotic medications (FGAs), were found to be effective in controlling the positive symptoms of schizophrenia spectrum disorders, allowing for improved organization and functioning (Taylor et al., 2012). Second-generation antipsychotics (SGAs) were created in part because of limited improvement in negative symptoms with the use of FGAs, as well as the frequency of extrapyramidal symptoms (EPS) that occurred with FGAs (Abou-Setta et al., 2012; Brissos et al., 2014; Diatta et al., 2007). The late 90s and early 2000s saw increases in AP prescriptions, and a preference emerged for newer APs and SGAs, thought to be due to the decreased occurrence of EPS (Diatta

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et al., 2007; Taylor et al., 2012; Verdoux et al., 2010).

Long-acting injectable (LAI) APs were first developed to decrease frequency of medication dosing associated with oral APs, thereby simplifying medication regimen, in the hope of increasing medication adherence (Greene et al., 2018; Maestri et al., 2018; Marcus et al., 2015). Adherence to AP medication can be difficult in those with schizophrenia spectrum diagnoses (i.e., schizophrenia, schizoaffective). For instance, psychotic symptoms, lack of insight, social barriers, and poor adherence can result in relapses and repeat hospitalizations (Brissos et al., 2014; Latorre et al., 2020). The first approved LAI was a depot formulation of Fluphenazine in 1968, and since that time, depot formulations have been approved in the United States for five other APs (Table 1).

Numerous observational studies have compared oral and LAI APs, and most highlight the comparative effectiveness of LAIs across multiple clinical outcomes. For instance, those prescribed LAI APs have been found to have lower hospital admission rates (Brissos et al., 2014; Fang et al., 2020; Latorre et al., 2020; Mahlich et al., 2020; Schoretsanitis et al., 2022), shorter hospital stays (Fang et al., 2020; Mahlich et al., 2020), fewer emergency room visits (Fang et al., 2020; Latorre et al., 2020), and increased outpatient appointment attendance (Latorre et al., 2020) when compared to those prescribed oral APs. Explanations center around increased medication adherence among those prescribed LAIs (Brissos et al., 2014; Subotnik et al., 2015).

Switching from oral to LAI APs can also be cost effective: Mahlich et al. (2020) found that despite the higher medication costs of LAIs, the reduction in days spent in the hospital after switching to LAIs resulted in a net decrease in cost for the healthcare system. Additionally, a large percentage of individuals who try LAIs prefer them to oral options, reporting increased convenience, effectiveness, and ability to pursue goals, as well as feeling more supported in their illness due to increased contact with providers (Brissos et al., 2014; Caroli et al., 2011). However, not all patients are offered LAI APs, in part due to perceived association of LAIs with increased illness severity, as well as presumed sufficient adherence to oral medications (Citrome et al., 2022).

Results from studies comparing FGAs and SGAs are more heterogeneous. Some have shown no significant differences between oral FGAs and SGAs when comparing outcomes such as quality of life, symptoms, adverse side effects, and associated costs of care (Abou-Setta et al., 2012; Jones et al., 2006). FGA vs. SGA LAIs may also be similar, with studies showing no significant differences in terms of adverse side effects, hospitalization rates, and rates of treatment discontinuation (Brissos et al., 2014; Stone et al., 2018). Conversely, some studies have shown preference of SGA over FGA LAIs, with both classes of LAIs being shown to be superior to oral AP treatment (Latorre et al., 2020; Marcus et al., 2015; Pacchiarotti et al., 2019). Abou-Setta et al. (2012) reasoned that while those taking SGAs have generally been found to have less risk of developing EPS, SGAs come with their own increased side effect risk profile, specifically sedation, hypotension, weight gain, metabolic changes, and sexual dysfunction.

Table 1
Antipsychotic Formulations and Approval Years.

Generic Name (Brand Name)	Oral Approval Year	LAI Formulation Availability	LAI Approval Year	Administration Frequency	FDA-Approved Indications	References
Chlorpromazine (Thorazine)	1954	No	N/a	N/a	Schizophrenia, behavioral problems associated with ODD/ADHD, acute psychosis, nausea/vomiting, acute intermittent porphyria, tetanus, intractable hiccups.	Ban, 2007
Perphenazine (Trilafon)	1957	Not in the United States	N/a	N/a	Schizophrenia, nausea/vomiting.	LiverTox.NIH.gov
Fluphenazine (Prolixin)	1959	Fluphenazine Decanoate	1968	Every 2–3 weeks	Psychotic disorders.	AccessData.FDA.gov; Crocq, 2015
Haloperidol (Haldol)	1967	Haloperidol Decanoate	1986	Monthly	Psychotic disorders, Tourette's syndrome.	ACS.org; Rapp et al., 1986
Clozapine (Clozaril)	1989	No	N/a	N/a	Schizophrenia, suicidal behavior in schizophrenia/schizoaffective disorder.	Newman & Newman, 2016
Risperidone (Risperdal)	1993	Risperdal Consta Perseris	2003 2018	Every 2–3 weeks Every 4 weeks	Schizophrenia, other psychotic disorders, acute/mixed mania, autism-related irritability in children, bipolar maintenance.	Drugs.com
Olanzapine (Zyprexa)	1996	Zyprexa Relprevv	2009	Monthly	Schizophrenia, acute agitation, acute/mixed mania, bipolar maintenance. When combined with fluoxetine (Symbyax), also bipolar depression and treatment-resistant depression.	Drugs.com; AccessData.FDA.gov
Quetiapine (Seroquel)	1997	No	N/a	N/a	Schizophrenia, acute mania, bipolar maintenance, bipolar depression, depression.	AccessData.FDA.gov
Ziprasidone (Geodon)	2001	No	N/a	N/a	Schizophrenia, acute agitation, acute/mixed mania, bipolar maintenance.	AccessData.FDA.gov
Aripiprazole (Abilify)	2002	Abilify Maintena Aristada	2013 2015	Monthly Monthly	Schizophrenia, acute/mixed mania, bipolar maintenance, depression, autism-related irritability in children, Tourette's disorder in children, acute agitation.	AccessData.FDA.gov; Otsuka.co
Paliperidone (Invega)	2006	Invega Sustenna Invega Trinza Invega Hafyera	2009 2015 2021	Monthly Every 3 months Every 6 months	Schizophrenia, schizoaffective disorder	AccessData.FDA.gov; Johnson & Johnson, 2022
Asenapine (Saphris)	2009	No	N/a	N/a	Schizophrenia, acute/mixed mania, bipolar maintenance.	AccdessData.FDA.gov
Iloperidone (Fanapt)	2009	No	N/a	N/a	Schizophrenia.	Montes & Rey, 2009
Lurasidone (Latuda)	2010	No	N/a	N/a	Schizophrenia, bipolar depression.	FDA.gov
Cariprazine (Vraylar)	2015	No	N/a	N/a	Schizophrenia, acute/mixed mania, bipolar depression.	Drugs.com
Brexpiprazole (Rexulti)	2015	No	N/a	N/a	Schizophrenia, treatment-resistant depression.	Drugs.com
Lumateperone (Caplyta)	2019	No	N/a	N/a	Schizophrenia, bipolar depression.	Drugs.com

While the existing literature largely focuses on the outcomes and associations with AP type and class, it generally fails to look at determinants of AP choice. There are also limited studies that consider estimates of illness severity. With these gaps in mind, the overall aim of this study was to examine clinical determinants of AP prescribing in a naturalistic cohort of patients with schizophrenia or schizoaffective disorder, who were psychiatrically hospitalized at an academic medical center in 2019–2020, and to compare clinical outcomes between diagnosis-matched LAI and oral AP groups, as well as between FGAs and SGAs within each group. Specific study aims included:

1. To compare prescribing trends between oral and LAI APs, as well as between FGAs and SGAs.
2. To examine the impact of AP choice on clinical outcomes, such as re-hospitalization rates over the course of a one-year follow-up.
3. To identify key clinical and sociodemographic factors that significantly predict AP choice, specifically LAI vs. oral AP, as well as FGA LAI vs. SGA LAI.

2. Materials and methods

The current study was conducted at the inpatient Behavioral Health Center at Westchester Medical Center Health System (WMC Health) in Valhalla, New York, an academic medical center affiliated with New York Medical College (NYMC). The protocol was granted exemption by the Institutional Review Board of NYMC (Protocol 14,446) and the Department of Quality Improvement at WMC Health. All adult psychiatric inpatients with a billing or principle diagnosis entered into the electronic medical record of schizophrenia or schizoaffective disorder, who received an LAI AP between January 1, 2019, and December 31, 2019, were included as the index group. An equal number of diagnosis-matched patients who consecutively received oral APs during the same time period were selected as the comparison group. Patients under the age of 18, those without one of the above diagnoses, and those who were prescribed therapeutic doses of more than one antipsychotic, using national accepted standards, were excluded from the study.

The records of included patients were obtained from the electronic medical record and analyzed for sociodemographic and clinical characteristics. Baseline length of admission (LOA) was utilized as the primary estimate of illness severity, providing a composite of acuity and complexity, with longer LOA having previously been associated with increased illness severity, chronicity, number of prior hospitalizations, and need for residential placement (Baeza et al., 2018; Pauselli et al., 2017; Wolff et al., 2015). Complexity of discharge was also used as an indicator of illness severity, providing possible insight into history of medication non-adherence and relapse (Pauselli et al., 2017). Patients were determined to have a complex discharge if they received any services - Assisted Outpatient Treatment (AOT), Assertive Community Treatment (ACT), Partial Hospitalization Program (PHP), or Personalized Recovery Oriented Services (PROS) - in addition to standard outpatient psychiatric care. Presence or absence of substance use disorder (SUD) was also recorded, due to an association found between co-occurring SUD and decreased treatment adherence in those with schizophrenia spectrum disorders (Brissos et al., 2014; Winklbaur et al., 2006). Number of readmissions, as well as number of returns to the psychiatric emergency department, was tracked for one year after the initial presentation. Sociodemographic information was recorded as indirect measures of illness severity and functioning in the community; characteristics such as being unemployed, being undomiciled, and/or lacking social support (as measured by relationship status) may introduce barriers to treatment adherence, thus resulting in more severe course of illness (Brissos et al., 2014; Degnan et al., 2018).

The data collectors (EG, SL) were trained on the record review instrument and were supervised by the study PI (SF). Inter-rater reliability on a subset of 10% of study records was high, exceeding 95%. Records on which there was disagreement were discussed and consensus reached by the study team.

Data were analyzed using SPSS software (IBM). Analyses included descriptive statistics (frequency, mean, standard deviation), Chi-square for group comparisons (i.e., LAI vs. oral; FGA vs. SGA) of categorical variables, and independent and one-sample t-tests for group comparisons of continuous variables (I.B.M., 2013). Logistic regression was conducted to identify independent predictors of prescribing LAIs and FGA LAIs (specifically Haloperidol), using sociodemographic (age, sex, ethnicity; employment, domicile, and relationship status) and clinical (LOA, co-occurring SUD) factors as predictor variables.

3. Results

3.1. Overall sample

There were 123 unique patients at the WMCHealth Network Behavioral Health Center who received LAIs in 2019. Half of this group had the diagnosis of Schizophrenia, with the remainder having the diagnosis of Schizoaffective Disorder (Table 2). This LAI index group was compared with 123 diagnosis-matched controls who received oral APs only during the same time period.

3.2. LAI vs. oral antipsychotics

When comparing the 123 patients who received LAIs with the matched cohort that received oral APs, we found that patients who received an LAI were less likely to be in a relationship or married. Additionally, there were significant differences in regards to ethnicity, with Hispanic patients comprising a smaller proportion of the LAI group than the oral group. There were no significant differences in age, sex, educational attainment, employment status, domicile status, or co-occurring substance use (Table 2). Those receiving LAIs were significantly more likely to receive an FGA compared to those prescribed oral APs.

In terms of direct illness severity indicators, patients who received an LAI were more likely than patients receiving oral APs to have a longer LOA and a complex discharge (Table 2). There was no significant difference in readmissions within 30 days or within one year between oral and LAI-treated patients. However, among the 78 patients who were readmitted within one year, those who had received LAI returned to the hospital sooner after discharge (Table 2).

In a multivariate logistic regression model predicting LAI vs. oral AP medication prescription, younger age, not being in a relationship, and having a longer LOA were the only independent predictors of receiving an LAI (Table 3).

3.3. FGA LAIs vs. SGA LAIs

Of the 123 patients who received an LAI, slightly less than half received an FGA, while the remainder received an SGA (Table 4). Specifically, 36 people (29.3%) received Haloperidol decanoate, 22 (17.9%) received Paliperidone palmitate, 26 (21.1%) received Aripiprazole monohydrate, 25 (20.3%) received Risperidone microspheres, and 15 (12.2%) received Fluphenazine decanoate.

When comparing sociodemographic characteristics between those who received FGA LAIs vs. SGA LAIs, we found that those who received an FGA LAI were significantly more likely to be undomiciled. On examination of individual LAIs, we found that those who received Aripiprazole monohydrate were less likely to be undomiciled compared to other LAIs (11.5% homeless; $p = 0.03$), whereas those receiving Fluphenazine decanoate were more likely to be undomiciled compared to other LAIs (60.0% undomiciled; $p < 0.01$). There were also significant differences among ethnicities (Table 4). Specifically, Aripiprazole monohydrate was disproportionately administered to White patients (46.2% of Aripiprazole monohydrate doses were administered to White patients; $p < 0.01$), while Haloperidol decanoate was disproportionately

Table 2
Long-acting injectable versus Oral Antipsychotics.

	Overall Sample (N = 246)	LAI (N = 123)	Oral (N = 123)	Sig (p, 95%)
Sociodemographic Factors				
Age (in years) (Mean, SD)	38.7, 15.3	38.2, 15.0	39.3, 15.6	0.55
Sex (N, % Female)	88 (35.8%)	47 (38.2%)	41 (33.3%)	0.43
Ethnicity (N, %)				0.04
White	83 (33.7%)	48 (39.0%)	35 (28.5%)	
Hispanic	52 (21.1%)	17 (13.8%)	35 (28.5%)	
Black	94 (38.2%)	49 (39.8%)	45 (36.6%)	
Other	17 (6.9%)	9 (7.3%)	8 (6.5%)	
Years of Education (Mean, SD)[a]	12.0, 1.6	12.1, 1.5	11.9, 1.7	0.60
Relationship Status (% In Relationship/Married)	35 (14.2%)	9 (7.3%)	26 (21.1%)	<0.01
Employment Status (N, % Currently Unemployed)[a]	208 (84.6%)	108 (87.8%)	100 (81.3%)	0.16
Housing Status (N, % Undomiciled)	59 (24.0%)	35 (28.5%)	24 (19.5%)	0.10
Clinical Factors				
Diagnosis (N, %)				1.0
Schizophrenia	126 (51.2%)	63 (51.2%)	63 (51.2%)	
Schizoaffective	120 (48.8%)	60 (48.8%)	60 (48.8%)	
Substance Use Disorder (N, % Yes)	104 (42.3%)	53 (43.1%)	51 (41.5%)	0.80
Category of AP (N, %)				<0.001
FGA	65 (26.4%)	51 (41.5%)	14 (11.4%)	
SGA	181 (73.6%)	72 (58.5%)	109 (88.6%)	
Length of First Admission (in days) (Mean, SD)[a]	18.4, 16.3	23.0, 20.0	13.9, 9.5	<0.001
Complex discharge (N, % Yes)	45 (18.3%)	37 (30.1%)	8 (6.5%)	<0.001
Readmissions				
Yes-Readmission 30 days (N, %)	23 (9.3%)	14 (11.4%)	9 (7.3%)	0.27
Yes-Readmission 1 year (N, %)	60 (24.4%)	29 (23.6%)	31 (25.2%)	0.77
Yes- ED Presentation within 30 Days	17 (6.9%)	10 (8.1%)	7 (5.7%)	0.45
Yes- ED Presentation within 1 year	22 (8.9%)	12 (9.8%)	10 (8.1%)	0.66
Days between Discharge and Readmission (Mean, SD)	86.5, 86.4	65.1, 62.5	107.0, 95.7	0.03
Insurance (N, % Medicaid/ Medicare)[a]	215 (90.3%)	109 (88.6%)	106 (92.2%)	0.35

[a] Indicating <246 patients included in overall analysis. Specific Ns as below: Years of Education – 203- Insurance – 238.

administered to Black patients (63.9% of Haloperidol decanoate doses were administered to Black patients; $p < 0.01$). There were no significant differences in age, sex, educational attainment, relationship status, or employment status between the FGA and SGA LAI groups. In terms of clinical factors, patients who received an FGA LAI were more likely to have a substance use disorder. There were no other statistically significant differences.

Within the LAI group, logistic regression revealed that the only significant independent predictors of receiving an FGA LAI was older age (Table 5).

Regarding clinical severity and outcomes, there was no significant difference between the. FGA and SGA LAI groups in terms of LOA, percent with complex discharge, readmission within 30 days, and readmission within one year.

3.4. Oral FGAs vs. oral SGAs

Of the 123 patients who received an oral AP, approximately 10% received an FGA, while the rest received an SGA (Table 6). In comparing those who received an oral FGA with those who received an oral SGA,

Table 4
First generation AP LAIs versus Second generation AP LAIs.

	Total Sample	FGA	SGA	Sig (p, 95%)
Sociodemographic Factors				
N	123			
Age (in years) (Mean, SD)	38.2, 15.0	40.9, 14.6	36.2, 15.1	0.09
Sex (N, % Female)	47 (38.2%)	18 (35.3%)	29 (40.3%)	0.58
Ethnicity (N, %)				0.03
Black	49 (39.8%)	28 (54.9%)	21 (29.2%)	
White	48 (39.0%)	17 (33.3%)	31 (43.1%)	
Hispanic	17 (13.8%)	4 (7.8%)	13 (18.1%)	
Other	9 (7.3%)	2 (3.9%)	7 (9.7%)	
Years of Education (Mean, SD)[a]	12.1, 1.5	12.2, 1.6	11.9, 1.4	0.30
Relationship Status (N, % In Relationship/Married)	9 (7.3%)	2 (3.9%)	7 (9.7%)	0.22
Employment Status (N, % Currently Unemployed)	108 (87.8%)	46 (90.2%)	62 (86.1%)	0.50
Housing Status (N, % Currently Undomiciled)	35 (28.5%)	20 (39.2%)	15 (20.8%)	**0.03**
Clinical Factors				
Diagnosis (N, %)				
Schizophrenia	63 (51.2%)	24 (47.1%)	39 (54.2%)	0.44
Schizoaffective	60 (48.8%)	27 (52.9%)	33 (45.8%)	
Substance Use Disorder (N, % Yes)	53 (43.1%)	28 (54.9%)	25 (34.7%)	**0.03**
Length of First Admission (in days) (Mean, SD)	23.0, 20.0	21.1, 18.5	24.3, 21.0	0.39
Complex discharge (N, % Yes)	37 (30.1%)	18 (35.3%)	19 (26.4%)	0.29
Readmissions				
Readmission 30 days (N, % Yes)	14 (11.4%)	8 (15.7%)	6 (8.3%)	0.21
Readmission 1 year (N, % Yes)	29 (23.6%)	14 (27.5%)	15 (20.8%)	0.39
Days between Discharge and Readmission (Mean, SD)	61.8, 62.7	74.9, 75.4	48.7, 45.7	0.26
Insurance (N, % Medicaid/ Medicare)	109 (88.6%)	47 (92.2%)	62 (86.1%)	0.30

[a] Indicating <123 patients included in overall analysis. Specific Ns as below: Years of Education – 102.

Table 3
Logistic regression- variables predicting LAI use.

Variable	Beta	Wald Statistic	Odds Ratio	95% Confidence Interval (Lower)	95% Confidence Interval (Lower)	Sig (p, 95%)
Age	−0.03	6.21	0.97	0.95	0.99	**0.01**
In Relationship	−0.93	4.30	0.40	0.17	0.95	**0.04**
Length of First Admission	0.06	18.15	1.06	1.03	1.09	**<0.001**

Gender, domicile status, race, substance use, and diagnosis were also included in the regression analysis and were not significant.

Table 5
Logistic Regression – Variables Predicting Specific LAIs.

Variable	Beta	Wald Statistic	Odds Ratio	95% Confidence Interval (Lower)	95% Confidence Interval (Lower)	Sig (p, 95%)
Variables Predicting FGA LAI Use						
Age	0.03	4.49	1.04	1.01	1.06	**0.03**
Variables Predicting Haloperidol LAI Use						
Age	0.04	4.47	1.04	1.01	1.08	**0.04**

Gender, domicile status, race, relationship status, substance use, length of admission, and diagnosis were also included in the regression analyses and were not significant.

those who received an oral FGA were more likely to be older and to be female (Table 6). There were no significant differences in ethnicity, years of education, relationship status, or domicile status. Patients who received an oral FGA were more likely to have a longer LOA and a complex discharge, when compared to the oral SGA group (Table 6).

There was no significant difference between the oral FGA and SGA groups in number of readmissions within 30 days; however, those who received an oral FGA were more likely to be readmitted within one year (Table 6). Overall, there were 9 patients (7.3%) in the oral AP group that were readmitted within 30 days, and 31 (25.2%) that were readmitted within 1 year. Among specific antipsychotics, only Risperidone, Clozapine, and Perphenazine were found to have significant relationships with readmission. Those taking Risperidone had fewer readmissions at 30 days and at 1 year than the average of all patients on oral APs (0% and 14.0%, p = 0.02 and p = 0.04, respectively). Patients on Clozapine had greater than average readmissions at both 30 days and one year (25% and 50%, p = 0.01 and p = 0.04, respectively), as did patients taking Perphenazine (33.3% and 66.7%, p = 0.01 and p = 0.02, respectively).

Table 6
First Generation versus Second Generation Oral Antipsychotics.

	Total Sample	FGA	SGA	Sig (p, 95%)
Sociodemographic Factors				
N	123			
Age (in years) (Mean, SD)	39.3, 15.6	47.4, 16.2	38.3, 15.3	**0.04**
Sex (N, % Female)	41 (33.3%)	8 (57.1%)	33 (30.3%)	**0.045**
Ethnicity (N, %)				0.48
Black	45 (36.6%)	4 (28.6%)	41 (37.6%)	
White	35 (28.5%)	6 (42.9%)	29 (26.6%)	
Hispanic	35 (28.5%)	4 (28.6%)	31 (28.4%	
Other	8 (6.5%)	0 (0.0%)	8 (7.3%)	
Years of Education (Mean, SD)	11.9, 1.7	11.2, 1.0	12.0, 1.8	0.16
Relationship Status (N, % In Relationship/Married)	26 (21.1%)	3 (21.4%)	23 (21.1%)	0.98
Employment Status (N, % Currently Unemployed)	100 (81.3%)	12 (85.7%)	88 (80.7%)	0.65
Housing Status (N, % Currently Undomiciled)	24 (19.5%)	3 (21.4%)	21 (19.3%)	0.85
Clinical Factors				
Diagnosis (N, %)				
Schizophrenia	63 (51.2%)	8 (57.1%)	55 (50.5%)	0.64
Schizoaffective	60 (48.8%)	6 (42.9%)	54 (49.5%)	
Substance Use Disorder (N, % Yes)	51 (41.5%)	4 (28.6%)	47 (43.1%)	0.30
Length of First Admission (in days) (Mean, SD)	13.9, 9.5	18.9, 11.7	13.3, 9.0	**0.04**
Complex discharge (N, % Yes)	8 (6.5%)	3 (21.4%)	5 (4.6%)	**0.02**
Readmissions				
Readmission 30 days (N, % Yes)	9 (7.3%)	1 (7.1%)	8 (7.3%)	0.98
Readmission 1 year (N, % Yes)	31 (25.2%)	7 (50.0%)	24 (22.0%)	**0.02**
Days between Discharge and Readmission (Mean, SD)	110.5, 99.6	125.9, 115.5	106.0, 96.8	0.65
Insurance (N, % Medicaid/ Medicare)	106 (92.2%)	13 (92.9%)	93 (92.1%)	0.92

*Indicating <123 patients included in overall analysis. Specific Ns as below.
- Years of Education – 101.

4. Discussion

4.1. Determinants of AP choice

One of the primary aims of this study was to explore predictors of AP choice in the acute treatment of psychiatric inpatients with a principle diagnosis of schizophrenia or schizoaffective disorder. We hypothesized that individuals with greater illness severity – those with longer LOA, complex discharge, and/or limited social supports – would more often be prescribed LAIs to help increase treatment adherence and reduce chance of relapse. We did find that longer LOA, likely indicating higher acuity and/or complexity of presentation, as well as being single, likely indicating lower level of social support, were both significant predictors of receiving an LAI, suggestive of appropriate identification and intervention for those in relative need of receiving an LAI. Being single may mean lack of reminders to take medication/attend appointments, decreased financial support to obtain medication, and/or lack of transportation to get to the pharmacy/appointments, all of which could increase the risk of medication non-adherence and relapse.

Younger age was also found to be a significant predictor of receiving an LAI. The reasons for this could include provider hesitancy to incorporate depot formulations with increasing age, given a potential concern for extended duration of side effects (Anagnostakis and Dex, 2010; van Os et al., 1997, 1999). Of note, most studies have not found significant differences in number or type of adverse side effects between oral and depot versions of APs, and depot formulations may be better tolerated due to lower variation in peak and trough levels (Brissos et al., 2014; Taylor, 2009). Provider hesitancy in prescribing LAIs to older individuals could also reflect cases of well-controlled symptoms on oral APs; prescribers are more likely to continue or resume medications to which patients have previously demonstrated good response and tolerability. The current literature is also increasingly favoring earlier use of LAIs, specifically following first psychotic episode, to mitigate more severe illness course; studies point to high risk of relapse following first psychotic episode, which could be mitigated with LAIs due to increased adherence (Abdel-Baki et al., 2020; Subotnik et al., 2015).

Regarding FGA LAIs vs. SGA LAIs, the only significant predictor of receiving an FGA was older age. There is limited literature regarding selection of LAI class based on age, however, Diatta et al. (2007) found that with oral APs, younger individuals were more likely to be prescribed an SGA, which they reasoned could correspond to long-standing well tolerated FGA treatments in older individuals. The same could be hypothesized for LAIs, as an individual with well-controlled symptoms on an oral FGA would be more likely to be transitioned to a depot formulation of the same AP agent.

4.2. Comparisons between AP groups

4.2.1. LAI compared to oral APs

In this naturalistic matched cohort study, we found that those in the LAI group likely had greater illness severity, with longer LOA, higher rates of complex discharge, and lower levels of social supports. Those with greater illness severity would be expected to have more frequent relapse and increased hospitalization rates, however we found no difference in overall readmission rates between the oral and LAI groups,

which implies effectiveness of LAIs in reducing readmission rates. Those who were readmitted in the LAI group were readmitted sooner than those in the oral group, which contrasts other studies (Maestri et al., 2018) but further supports the assumption of greater illness severity within the LAI group. Increased outpatient support (e.g. AOT or ACT), along with LAI medication, may have helped increase medication adherence and reduce relapse in this study. It is possible that a more significant difference between groups would become apparent with longer follow-up.

The LAI group was more likely to receive an FGA than the oral group, and possible explanations include the increased number of SGA oral options, and FGA LAIs having been approved decades earlier than SGA LAIs. Cost may also play a role, given that FGA LAIs are generally less costly; however, 90.3% of the patients included in this study had public health insurance (Medicare or Medicaid), which should somewhat mitigate impact of cost. Some literature shows that previous inpatient treatment, which could indicate greater illness severity, predicts prescription of FGA over SGA (Kroken et al., 2009). We also suspect that patients with a longer or more severe history of psychosis have been trialed on multiple antipsychotic agents, with possible treatment resistance, prompting prescribers to choose "high potency" antipsychotics such as Haloperidol. The notion that FGA is indicated in those with greater illness severity is not well supported in the literature, however this bias may persist.

4.2.2. FGA and SGA within the LAI group

When looking at FGA vs. SGA within the LAI group, our data revealed that those receiving FGAs were more likely to be undomiciled, which could again suggest a predisposition to prescribe "high potency" antipsychotics to those with risk factors for non-adherence (Barbui et al., 2006; Bolstad et al., 2011). Those receiving FGA LAIs were also more likely to have a co-occurring SUD, which contrasts other studies that have found that SGA LAIs or oral Clozapine may be preferred when treating those with co-occurring diagnoses, hypothesized to be due to their actions at more diverse receptor types and different side effect profile (Archibald et al., 2019; Winklbaur et al., 2006).

Our data also revealed an association between ethnicity and class of LAI, specifically that Aripiprazole monohydrate was more likely to be prescribed to White patients and Haloperidol decanoate was more likely to be prescribed to Black patients. Literature has shown that, for decades, non-White patients have been more likely to be prescribed an antipsychotic medication (Connolly, 2010), specifically an LAI (Aggarwal et al., 2012; Connolly, 2010; Covell et al., 2002; Wheeler et al., 2008), and an FGA (Connolly, 2010; Covell et al., 2002; Daumit et al., 2003), often at higher doses when compared to White patients (Connolly, 2010). Our logistic regression found that ethnicity was not a significant independent predictor of receiving FGA after accounting for other factors such as younger age and longer LOA, indicating that variables other than ethnicity may be responsible for the observed association.

4.2.3. FGA and SGA within the oral group

When looking at FGA vs. SGA within the oral group, our data found that those receiving FGAs were more likely to be older and female. Similar to the LAI group, older patients may have a longer treatment length that predates SGA options, and may have well-controlled symptoms on FGA (Diatta et al., 2007). Historically, some thought that females experienced increased side effects from APs compared males, and Anagnostakis and Dex (2010) found higher extrapyramidal side effects among females; however, the majority of studies have found that males are actually more likely to develop TD (van Os et al., 1997, 1999; Zhang et al., 2009) and have higher rates of abnormal involuntary movements (Anagnostakis and Dex, 2010; Zhang et al., 2009).

Those who received an oral FGA were more likely to have a complex discharge and longer LOA when compared to those prescribed oral SGA, which may reflect prescribing trends among specific providers.

When examining individual oral APs and readmission rates, only oral Risperidone had significantly fewer readmissions at both 30 days and one year, while both Clozapine and Perphenazine were found to have significantly more. This could potentially indicate that Risperidone is either somewhat more effective at managing symptoms, or that patients taking it have increased adherence to their medications. This is somewhat surprising, and contrasts prior literature, which found that Clozapine had the greatest impact on reducing readmissions (Baker and Aebi, 2017). It is important to note that the number of subjects in each individual oral AP category varied greatly, ranging from one (Asenapine) to 43 (Risperidone), and likely no strong conclusions can be made from this limited sample.

4.2.4. Limitations

This study had several limitations. We did not have access to an accurate account of patients' previous hospitalization histories prior to the study period, which would be an important indicator of illness severity (Baeza et al., 2018; Kroken et al., 2009; Pauselli et al., 2017; Wolff et al., 2015). We were also unable to determine whether patients had received LAIs prior to the study period, or for how long they had been prescribed LAIs if the LAI had been initiated prior to the index hospitalization. Information gathered was from WMC Health only, and therefore did not include the possibility of hospitalizations at other institutions during the study period; however, this behavioral health center was likely the primary option for these patients due to their community catchment area. This study took place at one site, which could limit its generalizability.

The current study also had no direct measure of medication discontinuation rates, which is thought to be one of the largest contributors to relapse. This study followed patients for one year following index discharge, similar to other studies (Fang et al., 2020; Mahlich et al., 2020). This may be a sufficient follow-up period, as other studies that have had longer follow-up found the mean time to relapse to be less than one year (Maestri et al., 2018; Emsley et al., 2013), and this number is consistent with quality data tracked from our institution. However, other studies estimate relapse rates in those with schizophrenia to be 28–37% at one year vs. 54% at three years (Moges et al., 2021), and we do not know if the readmission rate in this study (24% at one year) would change significantly with longer follow-up. Selection of LAI was also limited based on medications available in the hospital formulary, and so certain LAIs (such as Aripiprazole Lauroxil, other forms of risperidone (such as Perseris), or Olanzapine LAI (Zyprexa Relprevv)) were not utilized.

4.2.5. Strengths

Unlike many other studies, this study determined relative illness severity and explored potential predictors of AP choice using a comprehensive list of sociodemographic and clinical characteristics to. Like other studies, a control (oral AP) group was included to compare to the index (LAI) group, and group characteristics, as well as clinical outcomes, were compared. This was a naturalistic study, which is more likely to reflect true clinical practice, as patients consenting to clinical trials of LAIs may not be representative of those prescribed LAIs in real-world settings; specifically, they may have better baseline adherence and/or lower illness severity to be able to seek out and engage in a RCT (Brissos et al., 2014).

5. Conclusions

LAIs should be strongly considered in those with schizophrenia or schizoaffective disorders and increased social and/or clinical barriers to treatment. LAIs are an effective treatment option to equalize different relative illness severities among those with schizophrenia spectrum diagnoses, and they should be discussed in the shared decision-making process between patient and provider.

The choice of FGA vs. SGA should also rely on shared decision-

making, using past medical history, antipsychotic treatment history, and potential side effect profiles. More studies comparing FGA vs. SGA are necessary, to gain consensus over preferred treatment options.

Author contributions

Conceptualization and design: Sean Lynch, Emily Groenendaal, Stephen J. Ferrando, Lidia Klepacz, Rhea Dornbush; *Material preparation, data collection and analysis:* Sean Lynch, Emily Groenendaal, Stephen Ferrando; *Writing – original draft preparation:* Emily Groenendaal, Sean Lynch; *Writing – review and editing*: Sean Lynch, Emily Groenendaal, Stephen Ferrando; *Supervision*: Stephen Ferrando. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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