Contents lists available at ScienceDirect



Exploratory Research in Clinical and Social Pharmacy

journal homepage: www.elsevier.com/locate/rcsop

# Patterns and predictors of oral antipsychotic prescribing in adult patients with schizophrenia



OPEN ACCESS

# Nina Vadiei <sup>a,\*</sup>, Jasim El-Ali <sup>a</sup>, Joss Delaune <sup>a</sup>, Cecilia Wild <sup>a</sup>, Yi-Shao Liu <sup>b</sup>

<sup>a</sup> The University of Arizona, Department of Pharmacy Practice and Science, College of Pharmacy, Tucson, AZ, United States

<sup>b</sup> The University of Texas at Austin, Health Outcomes Division, College of Pharmacy, Austin, TX, United States

ARTICLE INFO	A B S T R A C T
Keywords: Schizophrenia Antipsychotic Patterns Predictors Adults Use	<i>Background:</i> Evidence increasingly suggests minimal differences in efficacy between oral antipsychotics for the pharmacologic treatment of schizophrenia. As a result, newer treatment guidelines avoid an algorithmic approach to antipsychotic selection and recommend treatment be determined on a case-by-case basis. <i>Objective:</i> To determine patterns and predictors of oral antipsychotic prescribing for adults diagnosed with schizophrenia. <i>Methods:</i> This is a retrospective, cross-sectional study using data from the National Ambulatory Medical Survey (NAMCS) from 2005 to 2016 and 2018. Treatment options were defined as a first-generation antipsychotic (FGA) second-generation antipsychotic (sGA), or no antipsychotic. Multivariable logistic regression analysis was conducted to identify predictors of antipsychotic treatment, adjusting for predisposing, enabling, and need factors. <i>Results:</i> The final study sample consisted of visits by 38,403 adults (unweighted <i>n</i> = 1932; age ≥ 18) diagnosed with schizophrenia in the United States. Risperidone, olanzapine, and quetiapine were the most prescribed antipsychotics Patients ≥ 65 years old were half as likely to be prescribed an SGA versus no antipsychotic (OR 0.44, 95% CI [0.31 0.61]). Patients with a higher number of chronic conditions also had lower odds of being prescribed an SGA or FGA versus no antipsychotic (OR 0.98 [0.97, 0.99]; OR [0.96 [0.96, 0.99]), while patients prescribed a higher number or medications had higher odds of being prescribed an SGA versus no antipsychotic, but no factor were associated with prescribing an SGA versus FGA. Future studies are needed to determine the reasoning behind differences in antipsychotic prescribing.

# 1. Introduction

Schizophrenia is estimated to affect 0.25% to 0.64% of people in the United States (US) and is one of the top fifteen leading causes of disability worldwide.<sup>1,2</sup> The American Psychiatric Association (APA) 2020 treatment guidelines strongly recommend that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.<sup>3</sup> Previously, the APA guidelines from 2004 had recommended second-generation antipsychotics (SGAs) be considered first-line over first-generation antipsychotics (FGAs); therefore, this is a significant change that may lead to changes in antipsychotic prescribing patterns over time. Because antipsychotic selection depends on many patient-specific factors, it is recommended that the treating clinician base treatment on the patient's treatment preferences and/or prior treatment responses following a discussion on the potential benefits and risks of different treatment options.<sup>3</sup>

The APA 2020 guidelines do not provide an algorithmic approach to antipsychotic selection owing to clinical trial design heterogeneity, limited clinical trial data for select antipsychotic medications, and limited headto-head comparisons of the many antipsychotic agents available.<sup>3</sup> Similarly, an evidence-based ranking of FGAs versus SGAs is not provided since there is no definitive evidence that one antipsychotic class will have consistently superior efficacy compared with the other.<sup>3</sup> Additionally, it is not possible to reliably predict the risk of side effects with one agent over another.<sup>3</sup> These findings are supported by a 2019 systematic review and meta-analysis which compared the efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia.<sup>4</sup> It concluded that while there are some efficacy differences between antipsychotics, most are gradual rather than discrete, with more marked differences in the types of side-effects experienced.<sup>4</sup> This supports the recommendation that clinicians weigh the risk versus benefit of these medications and consider their patient's specific comorbidities and preferences when prescribing.

Given antipsychotic prescribing is ultimately left to clinical discretion, it is important to evaluate both antipsychotic prescribing patterns and

\* Corresponding author at: The University of Arizona College of Pharmacy, Department of Pharmacy Practice and Science, 1295 North Martin Avenue, Tucson, AZ 85721, United States. *E-mail address:* vadiei@pharmacy.arizona.edu (N. Vadiei).

http://dx.doi.org/10.1016/j.rcsop.2022.100148

Received 9 January 2022; Received in revised form 20 May 2022; Accepted 2 June 2022

Available online xxxx

2667-2766/© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

modifiable/non-modifiable factors that may influence them. Determining disparities in antipsychotic prescribing will allow for future education on intrinsic biases that may affect antipsychotic selection. This study aimed to determine patterns and predictors of FGA and SGA prescribing in the US.

#### 2. Methods

#### 2.1. Study design

A retrospective, cross-sectional study design was utilized using data from the 2005–2016 and 2018 National Ambulatory Medical Care Survey (NAMCS). The University of Arizona Institutional Review Board determined that human subjects review was not required for this study.

## 2.2. Data source

NAMCS comprises nationally representative data related to ambulatory medical provisions and services from non-federally employed physician offices. Data on physician and patient characteristics, patient diagnoses, medications prescribed, and medical services are collected. The data is obtained via yearly surveys administered by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).<sup>5</sup> NAMCS weighs each visit to represent regional area and national estimates. Each visit is defined as an encounter with a physician or staff member working under the direct supervision of a physician to obtain healthcare services. A multistage probability design is used for data collection where initial probability samples are gathered from primary sampling units (PSUs) such as counties, groups of counties, or towns and townships. A probability sample of practicing physicians from each PSU is obtained to select from for patient visits. The entire physician sample is first split into 52 random subsamples of identical size, and then each subsample is randomly assigned to one of the 52 weeks in the survey year. For each assigned week, the physicians selected a systematic random sample of visits. A patient record form (PRF) is used during each visit to gather data on the physician, patient characteristics, diagnoses, delivery of therapeutics services, and prescribed medications. Per visit, up to 5 diagnosis codes and 30 prescription medications can be recorded in NAMCS. The NAMCS sampling framework makes it unlikely that the same individual is included in multiple visits.

## 2.3. Study sample

A total of 439,321 visits were collected from NAMCS from 2005 to 2016 and 2018. Data from 2017 were unavailable due to reported challenges in collecting electronic health record information that year. The final study sample included 38,403 adult visits (unweighted n = 1932; age  $\geq 18$ years) with a documented diagnosis of schizophrenia. The F-20 International Classification of Diseases (ICD)-10 codes were used to identify visits with a documented diagnosis of schizophrenia, including: F20, Schizophrenia; F20.1, Disorganized schizophrenia; F20.2, Catatonic schizophrenia; F20.3, Undifferentiated schizophrenia; F20.5, Residual schizophrenia; F20.8, Other schizophrenia; F20.81, Schizophreniform disorder; F20.89, Other schizophrenia; F20.9, Schizophrenia unspecified. Patients diagnosed with schizoaffective disorder, brief psychotic episode, or schizophrenia episode not otherwise specified were all excluded to provide greater study sample homogeneity.

# 2.4. Dependent variable

Schizophrenia treatment was defined as oral antipsychotic use, determined using generic drug codes and Multum Lexicon Codes. Treatment groups were defined as FGA, SGA, and no antipsychotic. The following oral FGAs were included: fluphenazine, haloperidol, chlorpromazine, loxapine, perphenazine, pimozide, thioridazine, and thiothixene. Oral SGAs included were: aripiprazole, asenapine, brexpiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

#### 2.5. Independent variables

The Anderson Behavioral Model (ABM) classifies independent variables as predisposing, enabling, and need factors.<sup>6</sup> Predisposing factors included: patient age (18–64 years;  $\geq$  65 years), gender (male; female), and race/ethnicity (Other race/multiple races, non-Hispanic; white-only, non-Hispanic; Black-only, non-Hispanic; Hispanic). Enabling factors included: insurance (Private; Public; Other) and area (Non-Metro; Metro). Need factors included: patient establishment (New Patient; Established Patient), visit reason (Chronic problem, routine; Other), number of medications (<5 medications;  $\geq$  5 medications), number of chronic conditions (<3 conditions;  $\geq$  3 conditions) and medical comorbidities (COPD; Diabetes; Hyperlipidemia; Hypertension). Factors that were hypothesized to impact prescribing patterns were included for data analysis. Cut-off points for the number of medications and chronic conditions were determined based on definitions of polypharmacy and multimorbidity used in previous studies.<sup>7–9</sup> Additional details regarding the independent variables of this study can be found in the NAMCS data documentation.<sup>10</sup>

#### 2.6. Statistical analysis

Ambulatory visits at the national level were reported as unweighted frequencies and weighted percentages. Multinomial regression was used with No antipsychotic and FGA as a reference group. The survey procedures (SURVEYFREQ and SURVEYLOGISTIC) with the cluster, stratum, and weighting variables provided by NAMCS were used to obtain national-level estimates across multiple years in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Per NAMCS recommendations, sample sizes  $\geq$  30 and  $\leq$  30% relative standard error (RSE) are required to determine a reliable national-level estimate.<sup>11</sup> Therefore, if any estimates in this study did not meet these criteria, the variable was left out of the multinomial regression.

#### 3. Results

According to NAMCS data from 2005 to 2016 and 2018, there were 38,403 recorded ambulatory visits (unweighted n = 1932; age  $\geq 18$ ) where schizophrenia was recorded as a diagnosis. Of these visits, 27,108 resulted in an antipsychotic prescription (70.1%, 95% CI [65.8, 75.4]); 23,702 SGA prescriptions (61.7%, 95% CI [58.6, 64.9]) and 3406 FGA prescriptions (8.9%, 95% CI [7.2, 10.5]). Yearly prescribing patterns between SGAs versus FGAs versus no antipsychotic can be found in the supplementary material. Predisposing, enabling, and need factors of the study group are provided in Table 1. Risperidone was the most prescribed antipsychotic (16.3%), followed by olanzapine (13.7%), quetiapine (13.6%), aripiprazole (11.0%), haloperidol (8.9%), and clozapine (6.2%). Prescribing prevalence of individual antipsychotics used for treating schizophrenia is provided in Table 2.

Multiple factors were associated with SGA prescribing versus no antipsychotic prescription (Table 3). Patients aged  $\geq$  65 were half as likely to be prescribed an SGA versus no antipsychotic (OR 0.44, 95% CI [0.31, 0.61]). Patients diagnosed with a higher number of chronic conditions had lower odds of being prescribed an SGA or FGA versus no antipsychotic (OR 0.98, 95% CI [0.97, 0.99]; OR [0.96, 95% CI [0.96, 0.99]). Patients prescribed more medications had 1.2 times the odds of being prescribed an SGA versus no antipsychotic (OR 1.2, 95% CI [1.1, 1.4]). Patients being seen for a routine visit had 2.5 times the odds of being prescribed an SGA versus no antipsychotic (OR 2.7, 95% CI [1.8, 4.0]) and almost twice the odds of being prescribed an FGA versus no antipsychotic (OR 2.1, 95% CI [1.1, 3.7]). There were no factors associated with a higher likelihood of prescribing an SGA versus FGA, though multiple variables could not be evaluated for statistical significance in the multinomial regression due to a sample size <30 for the FGA category.

#### 4. Discussion

As the number of antipsychotics available for treating schizophrenia continues to rise, it becomes increasingly important to monitor prescribing

#### Table 1

Demographic and Clinical Characteristics of Eligible Study Sample NAMCS (2005-2016, 2018).

	No antipsychotic		SGA		FGA			
	Wt%	95% CI	Wt%	95% CI	Wt%	95% CI	<i>p</i> -value	
Predisposing factors								
Age group								
18-64 years	27.0	[23.9,30.1]	64.0	[60.7.67.2]	9.0	[7.2,10.8]	< 0.001	
65 + years	43.4	[35.4,51.4]	48.6	[40.2,56.9]	N/A			
Gender								
Female	31.3	[27.0,35.5]	60.1	[55.9,64.4]	8.6	[6.4,10.8]	0.419	
Male	27.8	[23.8,31.8]	63.1	[59.0,67.3]	9.1	[6.9,11.3]		
Race/Ethnicity								
White	29.4	[26.1.32.7]	62.1	[58.6.65.6]	8.5	[6.5,10.5]	0.015	
Black	33.2	[26.0,40.4]	56.3	[49.4,63.6]	10.5	[6.7.14.2]		
Hispanic	28.7	[21.8,35.6]	59.8	[51.6,68.1]	11.5	[6.2,16.8]		
Others	N/A	2	80.3	[70.4,90.2]	N/A	L,		
Enabling factors	,			L	,			
Area								
Metro	29.8	[26.7,32.9]	61.9	[58.6,65.3]	8.3	[6.6,10.0]	0.195	
Non-metro	25.9	[15.0,36.9]	59.8	[49.0,70.6]	N/A	[]		
Insurance	2017	[1010,0015]	0,10	[1510], 010]				
Private	33.4	[26.6.40.2]	61.0	[53.9,68.0]	N/A		0.062	
Public	27.1	[23.1,31.1]	62.9	[59.0,66.9]	10.0	[7.9,12.0]	0.002	
Other	33.5	[25.6,41.4]	58.1	[50.0.66.2]	8.4	[4.8,12.0]		
Need factors	55.5	[23.0,41.4]	50.1	[50.0.00.2]	0.4	[4.0,12.0]		
Patient establishment								
New patient	39.7	[28.5,50.8]	55.7	[44.8,66.6]	4.6	[2.1,7.1]	0.034	
Established patient	28.8	[25.5,32.0]	62.1	[58.8,65.5]	9.1	[7.4,10.9	0.034	
Visit reason	20.0	[20.0,02.0]	02.1	[30.0,03.3]	9.1	[/.4,10.9		
Chronic prob., routine	24.7	[20.9,28.5]	66.2	[62.2,70.1]	9.2	[7.2,11.2]	< 0.001**	
Other	43.6		48.4		9.2 7.9		<0.001	
Number of medications	43.0	[37.0,50.2]	46.4	[41.6,55.3]	7.9	[4.7,11.2]		
<5 meds	31.8	[28.2,35.5]	59.7	[56.0,63.5]	8.5	[6 7 10 0]	0.014*	
<5 meds	22.0		67.9	- / -	8.5 10.2	[6.7,10.2]	0.014"	
≥ 5 meas Number of chronic conditions	22.0	[16.4,27.5]	67.9	[61.8,74.0]	10.2	[6.5,13.8]		
	07.0	[04.0.00.6]	(D F	[(0,0,(7,0]	0.0	[7 4 11 0]	.0.001	
<3 conditions	27.3	[24.0,30.6]	63.5	[60.0,67.0]	9.2	[7.4,11.0]	< 0.001	
≥3 conditions	41.9	[34.7,49.1]	51.3	[44.0,58.5]	N/A			
Depression	00.0	FOC 0 00 51	<i>(</i> <b>1</b> <i>i i</i>		0.7	FC 0 10 51	0.005	
No	29.9	[26.3,33.5]	61.4	[57.6,65.1]	8.7	[6.8,10.7]	0.895	
Yes	28.4	[22.8,34.0]	62.4	[56.1,68.8]	9.1	[6.1,12.2]		
Diabetes								
No	28.9	[25.8,32.0]	62.4	[59.2,65.7]	8.7	[6.9,10.4]	0.181	
Yes	35.3	[26.9,43.7]	53.4	[44.9,61.9]	N/A			
Hyperlipidemia								
No	28.2	[24.8,31.5]	62.7	[59.1,66.2]	9.2	[7.3,11.0][	0.066	
Yes	37.4	[28.9,45.9]	55.6	[47.5,63.7]	N/A			
Hypertension								
No	26.6	[23.2,30.1]	64.0	[60.3,67.7]	9.4	[7.5,11.3]	0.001**	
Yes	39.1	[32.7,45.4]	53.9	[47.5,60.4]	7.0	[3.9,10.1]		
Obesity								
No	29.5	[26.2,32.7]	61.5	[58.1,64.9]	9.0		0.854	
Yes	28.9	[19.6,38.2]	63.5	[54.6,72.5]	N/A			

Note: Wt% was noted as N/A if national-level estimates were unreliable (unweighted n < 30). Asterisks represent statistical significance between the three groups based on chi-square tests. Statistical significance not reported for groups with a sample size <30. Abbreviations: SGA: second-generation antipsychotic; FGA: first-generation antipsychotic; Wt%: Weighted percentage. \*\*\* p < 0.001; \*\* 0.001  $\leq p < 0.01$ ; \*0.01  $\leq p < 0.05$ .

Table 2	
Prescribing Prevalence of Individual Antipsychotics NAMCS	
(2005–2016, 2018).	

2000 2010, 2010).				
Antipsychotic	Wt% (95% CI)			
Risperidone	16.3 (14.2,18.4)			
Olanzapine	13.7 (11.8,15.7)			
Quetiapine	13.6 (11.7,15.5)			
Aripiprazole	11.0 (9.3,12.8)			
Haloperidol	8.9 (7.0,10.8)			
Clozapine	6.2 (4.3,8.1)			
Ziprasidone	6.1 (4.6,7.7)			
Paliperidone	3.6 (2.5,4.8)			
Fluphenazine	3.4 (2.3,4.5)			
Perphenazine	1.8 (1.1,2.6)			

Note: Antipsychotics with a sample size <30 were not included.

patterns of these agents. This study showed that SGAs (particularly risperidone, olanzapine, and quetiapine) are used more often than FGAs. Each of these agents has substantial differences in the types of side-effects experienced,<sup>4</sup> which is significant considering side-effects are cited as one of the leading causes of medication nonadherence.<sup>12,13</sup> To promote treatment adherence and optimize patient outcomes, new treatment guidelines recommend a patient-centered approach in antipsychotic prescribing and no longer recommend a specific class be used first-line.<sup>3</sup> As such, it is also important to determine what factors influence antipsychotic prescribing patterns. While previous studies have focused on racial disparities related to antipsychotic prescribing,<sup>14–17</sup> this study sought to determine what additional factors may impact this.

Patients aged  $\geq$  65 diagnosed with schizophrenia were less likely to be prescribed an SGA compared to no antipsychotic. One reason for this may be the boxed warning for increased risk of death in adults diagnosed with dementia.<sup>18–20</sup> Because this dataset did not allow for the assessment of certain comorbid diagnoses that may have influenced prescribing

#### Table 3

Multinomial Logistic Regression NAMCS (2005-2016, 2018).

	SGA vs. no antipsychotic			FGA vs. no antipsychotic			SGA vs. FGA		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Predisposing factors									
Age group									
65+ yrs. vs 18–64 yrs	0.435	[0.309,0.612]	***	0.484	[0.250,0.936]		0.900	[0.461,1.759]	
Gender									
Male vs. female	1.144	[0.879,1.489]		1.128	[0.749,1.700]		1.014	[0.717,1.435]	
Race/Ethnicity									
Hispanic vs. Black	1.414	[0.809,2.473]		1.538	[0.747,3.167]		0.919	[0.460,1.837]	
White vs. Black	1.209	[0.824,1.775]		0.883	[0.523,1.493]		1.369	[0.847,2.213]	
Enabling Factors									
Area									
Non-metro vs. Metro	1.085	[0.601,1.959]		1.920	[0.855,4.309]		0.565	[0.307,1.041]	
Insurance									
Private/vs. Public	0.850	[0.577,1.250]		0.542	[0.315,0.935]		1.566	[0.949,2.585]	
Others vs. Public	0.934	[0.632,1.380]		0.917	[0.512,1.640]		1.019	[0.597,1.736]	
Need Factors									
Patient establishment									
Established vs. New	0.881	[0.513,1.512]		1.747	[0.782,3.904]		0.504	[0.240,1.061]	
Visit reason									
Routine vs. not routine	2.670	[1.775,4.016]	***	2.066	[1.146,3.725]	*	1.292	[0.713,2.341]	
Number of medications									
$\geq$ 5 meds vs. <5 meds	1.202	[1.006,1.436]	*	1.186	[0.997,1.410]		1.013	[0.968,1.061]	
Number of chronic conditions									
$\geq$ 3 conditions vs. <3 conditions	0.984	[0.970,0.997]	*	0.976	[0.956,0.998]	*	1.007	[0.982,1.033]	

Note: Based on 1932 adults (weighted N = 38,403) adults (age  $\geq 18$  years) with schizophrenia between 2005 and 2015, 2016, and 2018.

Asterisks represent statistically significant group differences by type of treatment compared to the reference group based on multinomial logistic regression at  $\alpha$  level of 0.05. The reference group for the dependent variable in the multinomial logistic regression was "no antipsychotic" for the first two columns and "typical antipsychotic" for the last column. Statistical tests were not performed to evaluate the significance of groups with a sample size <30. Abbreviations: SGA: second-generation antipsychotic; FGA: first-generation antipsychotic.

\*\*\*p < 0.001; \*\*0.001  $\leq p < 0.01$ ; \*0.01  $\leq p < 0.05$ .

(e.g., neurocognitive disorders, mood disorders), an association between these specific chronic conditions and antipsychotic prescribing patterns could not be determined. Since schizophrenia is associated with an elevated risk of developing Alzheimer's disease, 21,22 and because SGAs are commonly used for treating behavioral and psychological symptoms of dementia (BPSD),<sup>19,23,24</sup> these findings may correspond to a reduction in using these agents over alternative non-antipsychotic options. However, this data alone cannot determine this, and additional studies are needed to determine patterns and predictors of antipsychotic use in patients with both schizophrenia and dementia. These findings are similar to a previous 2013 study by Wang et al. that utilized Medical Expenditure Panel Survey data from 2004 and 2005.<sup>25</sup> In the study by Wang et al., patients aged  $\geq$ 65 were 0.63 times as likely to use antipsychotics as younger patients.<sup>25</sup> This suggests this use pattern may have already existed before the antipsychotic warning of increased death risk in dementia, though this study only reported on antipsychotic use patterns without specifying indications. To the best of our knowledge, the current study is the first to report on antipsychotic prescribing patterns in patients with schizophrenia.

Older adults with schizophrenia may also be less likely to be prescribed an SGA compared to no antipsychotic due to multimorbidity worsening the probability or extent of experiencing adverse effects with SGAs.<sup>26</sup> For example, there is a higher prevalence of metabolic disorders in older adults compared to younger adults.<sup>27,28</sup> Older adults also have a higher risk of experiencing dizziness/falls.<sup>26</sup> As such, SGAs may be avoided more in this population due to increased fall risk and/or worsening metabolic disorders.<sup>29–33</sup> This corresponds with the finding that patients with a higher number of chronic conditions also had a lower likelihood of being prescribed an SGA or FGA versus no antipsychotic. While ongoing pharmacologic treatment may help patients with schizophrenia achieve long-term remission and functional recovery,<sup>34</sup> there may come a time when the prescriber determines the risk of adverse effects associated with ongoing SGA use exceeds the potential benefit. Therefore, while it makes sense that patients seen for a routine visit are more likely to be prescribed an SGA or FGA versus no antipsychotic compared to non-routine visits, it appears older adults with certain comorbidities or risk factors may be less likely to receive ongoing treatment. This situation may also occur in cases where the prescriber disagrees with a previously documented diagnosis of schizophrenia, though this study did not find a difference in prescribing patterns between established and new patients.

Patients on a higher number of medications were more likely to be prescribed an SGA than no antipsychotic. Perhaps this is because patients on a higher number of medications at baseline may be more agreeable to starting an antipsychotic medication for treatment of schizophrenia, or other potential uses, than patients who are on fewer medications and do not wish to take medication(s). Alternatively, patients with a diagnosis of schizophrenia that are prescribed a higher number of medications may have a higher chance of experiencing distressing medication side effects that result in antipsychotic prescribing to treat both their schizophrenia and other symptoms (e.g., insomnia, anxiety).<sup>35,36</sup> However, this study did not account for potential off-label uses.

As previously mentioned, many studies have reported on racial/ethnic disparities in SGA prescribing.<sup>14–17</sup> Specifically, gaps in SGA versus FGA prescribing reportedly decreased during the 1990s but persisted for Black patients with psychotic disorders.<sup>14</sup> In the study by Daumit et al., which also utilized NAMCS from 1992 to 2000,<sup>14</sup> Black patients were half as likely to be prescribed an SGA compared to White patients. However, the odds of receiving an SGA prescription continued to increase for both Black and Hispanic patients over time.<sup>14</sup> A more recent 2015 study by Cook et al., which utilized NAMCS data from 2005 to 2010, reported ongoing racial disparities in FGA versus SGA prescribing, with Black patients having 1.48 times the odds of being prescribed an FGA compared to White patients.<sup>17</sup> This study did not find a significant difference in SGA versus FGA prescribing between Black and White patients, suggesting that racial disparities in outpatient antipsychotic prescribing for patients with schizophrenia have improved over the past decade.

There was also no significant difference in antipsychotic class prescribing between metropolitan and non-metropolitan regions. However, a reliable association was not determined since only 28 patients in the nonmetropolitan group were prescribed an FGA. The aforementioned study by Wang et al., which reported patterns and predictors of antipsychotic use in the US using Medical Expenditure Panel Survey data from 2004 and 2005, found that urban residents were 1.87 times as likely as rural residents to use SGAs.<sup>25</sup> No US studies since then have reported on urban-rural differences in SGA versus FGA prescribing rates. However, a recent 2019 study investigating psychotropic treatment patterns in patients with schizophrenia in China did not find a significant difference in SGA or FGA prescribing rates between rural/urban areas.<sup>37</sup> More studies are needed to determine whether regional disparities in outpatient antipsychotic prescribing for patients with schizophrenia have improved over time.

The following limitations should be taken into consideration when interpreting these findings. Data from NAMCS for patients diagnosed with schizophrenia was only available until 2018; therefore, antipsychotic prescribing patterns may have changed since then. Future studies should seek to determine prescribing patterns and predictors following the most recent practice guidelines release.<sup>3,38</sup> These findings may not be generalizable to prescribing patterns in inpatient facilities since NAMCS reports on data from non-federally funded outpatient health facilities. The small sample size may have contributed to a possible underpowering in statistical analysis (unweighted N = 1932). Misclassification or underreporting of schizophrenia may have occurred. Coding errors, reporting errors, and interviewer effects should also be considered. There was no adjusting for off-label uses of antipsychotics such as for sleep, anxiety, or behavioral disturbances in neurocognitive disorders. Additionally, comorbidities from NAMCS that may have influenced antipsychotic prescribing, such as bipolar disorder and anxiety disorders, could not be captured. Information regarding antipsychotic dose was also unavailable, and other patient-specific factors that influence prescribing, such as duration and severity of schizophrenia, activities of daily living, and functional status. This study did not evaluate antipsychotic polypharmacy prescribing patterns, though it appears some patients in this sample were prescribed >1 antipsychotic since the total number of antipsychotic prescriptions was higher than the total number of visits resulting in an antipsychotic prescription. Lastly, causal inferences cannot be established due to the retrospective, crosssectional study design.

#### 5. Conclusions

Roughly three-fourths of patients with schizophrenia seen in an ambulatory care setting were prescribed an antipsychotic. SGAs were prescribed more often than FGAs, but no individual-level factors predicted whether there were higher odds of prescribing an SGA over an FGA. On the other hand, multiple individual-level factors predicted whether patients were prescribed a specific antipsychotic class versus no antipsychotic. Future studies should seek to understand the reasons for antipsychotic prescribing pattern differences and what impact this may have on clinical outcomes.

#### Disclosures and acknowledgements

The authors declare that they have no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### **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.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.rcsop.2022.100148.

#### References

- National Institute of Mental Health. Schizophrenia. Available: https://www.nimh.nih. gov/health/statistics/schizophrenia 2018. Accessed November 5, 2021.
- Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211–1259.
- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Focus (Am Psychiatr Publ) 2020;18:493–497.
- Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019;394:939– 951.
- National Centers for Disease Control and Prevention: National Center for Health Statistics. Ambulatory Health Care Data. Available: https://www.cdc.gov/nchs/ahcd/index. htm. Accessed November 5, 2021.
- Anderson JG, Bartkus DE. Choice of medical care: a behavioral model of health and illness behavior. J Health Soc Behav 1973;14:348–362.
- Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and deprescribing. Am Fam Physician 2019;100(1):32–38.
- Fortin M, Stewart M, Poitras M, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. Ann Fam Med 2012;10(2):142–151.
- Lee ES, Lee PSS, Xie Y, Ryan BL, Fortin M, Stewart M. The prevalence of multimorbidity in primary care: a comparison of two definitions of multimorbidity with two different lists of chronic conditions in Singapore. BMC Public Health 2021;21(1):1409.
- Centers for Disease Control and Prevention. Survey NAMCS (2015) Data documentation. Available: ftp://ftp.cdc.gov/pub/Health\_Statistics/NCHS/Dataset\_Documentation/ NAMCS. Accessed September 25, 2021.
- Centers for Disease Control and Prevention. Ambulatory Health Care Data: Reliability of Estimates. Available: https://www.cdc.gov/nchs/ahcd/ahcd\_estimation\_reliability.htm 2015. Accessed November 5, 2021.
- Velligan DI, Sajatovic M, Hatch A, Kramata P, Docherty JP. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence 2017;11:449– 468.
- Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A. Psychotropic medication nonadherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. Syst Rev 2020;9:17.
- Daumit GL, Crum RM, Guallar E, et al. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. Arch Gen Psychiatry 2003;60:121–128.
- Kuno E, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. Am J Psychiatry 2002;159:567–572.
- Puyat JH, Daw JR, Cunningham CM, et al. Racial and ethnic disparities in the use of antipsychotic medication: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2013;48:1861–1872.
- Cook TB, Reeves GM, Teufel J, Postolache TT. Persistence of racial disparities in prescription of first-generation antipsychotics in the USA. Pharmacoepidemiol Drug Saf 2015;24: 1197–1206.
- US Food and Drug Administration. Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Available: https:// wayback.archive-it.org/7993/20170113112252/http://www.fda.gov/Drugs/ DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053171. htm. Accessed November 25, 2021.
- Rubino A, Sanon M, Ganz ML, et al. Association of the US Food and Drug Administration antipsychotic drug boxed warning with medication use and health outcomes in elderly patients with dementia. JAMA Netw Open 2020;3, e203630.
- Ralph SJ, Espinet AJ. Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. J Alzheimers Dis Rep 2018;2:1-26.
- Kochunov P, Zavaliangos-Petropulu A, Jahanshad N, et al. A white matter connection of schizophrenia and Alzheimer's Disease. Schizophr Bull 2021;47:197–206.
- Cai L, Huang J. Schizophrenia and risk of dementia: a meta-analysis study. Neuropsychiatr Dis Treat 2018;14:2047–2055.
- Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA 2012;308:2020–2029.
- Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry 2016;173:543–546.
- Wang CC, Farley JF. Patterns and predictors of antipsychotic medication use among the US population: findings from the Medical Expenditure Panel Survey. Res Soc Adm Pharm 2013;9:263–275.
- 26. Salive ME. Multimorbidity in older adults. Epidemiol Rev 2013;35:75-83.
- Sinclair A, Viljoen A. The metabolic syndrome in older persons. Clin Geriatr Med 2010;26:261–274.
- Morley JE. The metabolic syndrome and aging. J Gerontol A Biol Sci Med Sci 2004;59: 139–142.
- Gautam S, Meena PS. Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics. Indian J Psychiatry 2011;53:128–133.

#### N. Vadiei et al.

- Abo Alrob O, Alazzam S, Alzoubi K, et al. The effect of long-term second-generation antipsychotics use on the metabolic syndrome parameters in Jordanian population. Medicina (Kaunas) 2019;55.
- Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7:64–77.
- 32. Tandon R, Lenderking WR, Weiss C, et al. The impact on functioning of second-generation antipsychotic medication side effects for patients with schizophrenia: a worldwide, cross-sectional, web-based survey. Ann General Psychiatry 2020;19:42.
- Khasawneh FT, Shankar GS. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. Cardiol Res Pract 2014;2014, 273060.
- Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. Schizophr Bull 2013;39:1363–1372.
- Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiol Drug Saf 2011;20:177–184.
- Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and metaanalysis. JAMA 2011;306:1359–1369.
- Hou CL, Wang SB, Wang F, et al. Psychotropic medication treatment patterns in community-dwelling schizophrenia in China: comparisons between rural and urban areas. BMC Psychiatry 2019;19:242.
- London: National Institute for Health and Care Excellence (UK). 2019 exceptional surveillance of psychosis and schizophrenia in adults: prevention and management (NICE guideline CG178). 2019.