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Quetiapine and olanzapine misuse prevalence in a US general population sample

Kirk E Evoy, PharmD, BCACP, BC-ADM, CTTS[1]; Shelby Humpert, PharmD[2]; Sorina Torrez, PharmD[3]; Haneen Hussein, PharmD[4]; Jordan R Covvey, PharmD, PhD, BCPS[5]

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Abstract

Introduction: Second-generation antipsychotics (SGA) are associated with misuse potential; however, there are limited data describing the prevalence and characteristics of this misuse. This study was conducted to identify and describe quetiapine and olanzapine misuse among US adults.

Methods: This cross-sectional survey questionnaire was conducted online using Qualtrics research panel aggregator service to identify a quota-based sample of respondents constructed to mimic the general US population aged 18 to 59 years, with regards to gender, geographic region, ethnicity, income, and education level. Misuse was defined as using quetiapine or olanzapine for treatment outside of medical recommendations, for reasons other than a diagnosed medical condition, or obtaining without a prescription. A logistic regression was used to identify factors associated with SGA misuse, incorporating relevant covariates.

Results: Among 1843 total respondents, 229 had a history of quetiapine or olanzapine use. Misuse prevalence was estimated to be 6.3% (95% CI: 5.2, 7.5%). Although most respondents (~70%) using quetiapine or olanzapine reported doing so to treat a diagnosed medical condition, those misusing them most commonly did so because prescribed medications failed to relieve their symptoms. Misuse was commonly reported (~50%) concomitantly with opioids, benzodiazepines, or alcohol. Factors significantly associated with quetiapine or olanzapine misuse included employment (OR = 4.64), previous substance use disorder treatment (OR = 2.48), and having riskier attitudes toward medication misuse (OR = 1.23).

Discussion: Misuse of quetiapine and olanzapine, while fairly limited in prevalence, appears to be primarily associated with under-treatment of existing medical conditions.

Keywords: olanzapine, quetiapine, antipsychotic, drug misuse, diversion

[1] Clinical Associate Professor, The University of Texas at Austin College of Pharmacy, Austin, Texas; Clinical Associate Professor, The University of Texas Health San Antonio School of Medicine, San Antonio, Texas; Clinical Pharmacist, University Health, San Antonio, Texas, ORCID: https://orcid.org/0000-0003-0913-7145; [2] Pharmacy Resident, The University of Texas at Austin College of Pharmacy, Austin, Texas, ORCID: https://orcid.org/0000-0003-2245-5973; [3] Pharmacy Resident, The University of Texas at Austin College of Pharmacy, Austin, Texas, ORCID: https://orcid.org/0000-0002-3888-3457; [4] Pharmacy Resident, University of Chicago Medicine, Chicago, IL, ORCID: https://orcid.org/0000-0001-6590-4682; [5] (Corresponding author) Associate Professor, Duquesne University School of Pharmacy, Pittsburgh, Pennsylvania, covveyj@duq.edu, ORCID: https://orcid.org/0000-0003-2913-2042

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Introduction

The second-generation antipsychotics (SGA) quetiapine and olanzapine are serotonin-dopamine antagonists approved by the FDA to treat bipolar disorder and schizophrenia.[1,2] They may also be used off-label to treat a variety of other conditions, including generalized anxiety disorder, insomnia, and agitation/delirium, among others.[3] SGAs are not classified as controlled substances by the United States (US) Drug Enforcement Administration and are traditionally considered to have limited misuse potential. However, anecdotal reports indicate that SGAs are misused for their

sedative, calming, and anxiolysis effects,[4,5] either alone or together with other substances in order to achieve desired psychotropic effects.[5,6]

The pharmacologic rationale for SGA misuse may relate to effects on the H_1 receptor antagonism (sedation) or alpha-adrenergic antagonism (anxiolytic), and misuse is hypothesized primarily as a means of self-treatment for undiagnosed or undertreated illnesses, though some also report experiencing desirable effects from the SGAs themselves.[7,8] Early case reports identified misuse in institutionalized systems, such as prisons and inpatient psychiatric facilities,[8,9] but further evidence has revealed misuse within other populations as well, including those with polysubstance use disorders.[8] Recent population health evidence from Australia and the United States have also identified growing patient harm associated with increased use of SGAs, including significant increases in quetiapine-related emergency department (ED) visits and deaths.[6,10]

As the United States grapples with the ongoing opioid overdose crisis and implements strategies to reduce associated harms, there is interest in further understanding the misuse potential of other classes of medications. Recognizing such risks allows clinicians to be more proactive in their approaches to prescribing, dispensing, and monitoring medications, and enhances their ability to engage patients in meaningful conversations regarding misuse and undertreated or undiagnosed medical conditions. Reports of misuse and patient harm related to the SGAs, particularly quetiapine and olanzapine,[11] have increased, yet a full understanding of the prevalence of this misuse, as well as details regarding patterns of misuse (eg, frequency, use with other substances, motivations for use) within the US general population remains relatively unknown. Accordingly, the objective of this study was to identify and describe misuse of quetiapine and olanzapine among US adults.

Methods

Study Design and Sampling

The study used a cross-sectional, English-language, survey questionnaire, administered online in May 2019 to a sample identified through the Qualtrics® panel aggregator service (Qualtrics, Provo, Utah). The process was described previously[12] and used a quota-based sample composed of respondents aged 18 to 59 years similar to the US population with regards to gender, geographic region, ethnicity, income, and education level. The total sample size was informed using a 95% confidence level, a 2.5% margin of error, and an estimated population of 2.5 million patients taking either olanzapine or quetiapine.[13] Participation was voluntary, anonymous, and compensated, with specific compensation per individual respondent set by Qualtrics. Potential respondents were offered the opportunity to participate twice (separated by 24 to 48 hours) until predefined demographic quotas were achieved. Previous healthcare analyses have used this service to obtain research samples, with standardized methods used to reduce selection bias and to improve data integrity.[14-17]

Questionnaire

An investigator-designed questionnaire was drafted, piloted, and revised in several iterations by the research team. The questionnaire (including closed-ended and Likert-type items) collected respondent clinical/demographic data, attitudes regarding medication/substance use, and queried respondents' use of several different drugs of potential misuse, with items regarding their frequency and patterns of use. The focus of the present analysis was SGA misuse, specifically focused on olanzapine and quetiapine. Some survey items probed data regarding either SGA individually, while others queried data on both SGAs collectively. A set of 6 items focused on measuring respondents' knowledge, attitudes, and beliefs about medication and substance use (Table 1); each item included a 5-point scale ranging from *Strongly Agree* (5) to *Strongly Disagree* (1). From these data, a total attitudinal risk score was calculated, ranging from 6 to 30, with higher scores indicating higher acceptability of behaviors deemed more *risky* related to medication misuse, such as endorsing the safety and appropriateness of prescription drugs for recreational use and dose self-titration, and ease of obtainment outside of usual medical channels, such as a pharmacy. The risk-related items, like the rest of the questionnaire, were investigator-designed and not previously validated.

Data Analysis

Survey data from Qualtrics were exported into Microsoft Excel (Redmond, Washington) and IBM SPSS Statistics (Armonk, New York) for analysis. An overall estimate of olanzapine and quetiapine misuse was ascertained, which was affirmatively assigned if the respondent disclosed at least 1 of the following via a series of items: (1) using SGAs on their own to treat symptoms outside of medical recommendations or guidance, (2) using SGAs for reasons other than a diagnosed medical condition (such as getting high or for pleasure), or (3) obtaining SGAs without a prescription from a source outside of the medical system (eg, family, friend, or on the street), regardless of reason for use. Descriptive analysis for demographic and clinical characteristics were reported for the respondents as a whole, as well as those reporting SGA use, split by whether their use includes report of misuse or not. Bivariable statistical comparisons were conducted for the latter 2 categories of respondents reporting SGA use. Further descriptive analysis

TABLE 1: Survey questionnaire[a]

Item	Responses
Medication Use Risk Score	
Taking prescription medications for recreational purposes is safer than illegal drugs.	• Strongly agree • Agree • Neutral • Disagree • Strongly disagree
Taking a prescription medication (whether yours or someone else's) without a healthcare provider's knowledge is sometimes okay to treat symptoms.	
Taking a prescription medication (whether yours or someone else's) without a healthcare provider's knowledge is sometimes okay for recreational purposes.	
Taking a larger dose of prescription medication than has been prescribed is sometimes okay to treat symptoms.	
Taking a larger dose of prescription medication than has been prescribed is sometimes okay for recreational purposes.	
Prescription medications are easy to obtain outside of using a prescription at a pharmacy (eg, online, from family, friends, or dealers).	
Information on Medication Use and Misuse	
For the following, please indicate if you have ever taken the medication (past or present). SELECT ALL THAT APPLY.	• Pregabalin (Lyrica) • Gabapentin (Neurontin, Horizant) • Quetiapine (Seroquel) • Olanzapine (Zyprexa) • Duloxetine (Cymbalta) • Hydroxyzine (Atarax) • Sertraline (Zoloft) • None of the above
For [insert drug] please indicate how you have obtained it (past or present). SELECT ALL THAT APPLY.	• It was prescribed to me by a healthcare provider • I received it from friends or family members • I bought it from a dealer, on the street, or on the internet
What is/was your primary reason for taking [insert drug]? SELECT ALL THAT APPLY.	• To treat a diagnosed medical condition under a healthcare provider's recommendation • To treat symptoms outside of a healthcare provider's recommendations (eg, based on my own judgement) • For recreational purposes (eg, getting high, increased sociability, pleasure or performance enhancement) • To take together with other drugs/substances to increase/enhance the other drug/substance's effects • Other (please specify)
Which of the following best describes how often you have used [insert drug] for reasons OTHER than a diagnosed medical condition under a healthcare provider's recommendation?	• Once or twice in my lifetime • Yearly • Monthly • Weekly • Daily
Have you ever used any of the following drugs/substances together with [insert drug] recreationally? SELECT ALL THAT APPLY.	• Opioids (eg, Vicodin, Percocet, Oxycontin, methadone, fentanyl, heroin, Suboxone, etc.) • Benzodiazepines (eg, Xanax, Valium, Klonopin, etc.) • Alcohol • Another medication (please specify) • None - I use it alone
Have you ever used any of the following drugs/substances together with [insert drug] to increase/enhance its effects? SELECT ALL THAT APPLY.	

TABLE 1: Survey questionnaire[a] (continued)

Item	Responses
Have you ever taken [insert drug] for any of the following reasons? SELECT ALL THAT APPLY.	• You were no longer able to obtain another medication/drug you used to take • The medications prescribed by your healthcare provider were not relieving your symptoms • You were experiencing symptoms of withdrawal from [insert drug] itself • You were coping with symptoms of withdrawal from other drugs/substances • None of the above
When you take pregabalin (Lyrica) recreationally, what dose do you usually take?	• Less than or equal to 150 mg • 151 to 300 mg • 301 to 450 mg • 451 to 600mg • Greater than 600 mg
When you take gabapentin (Neurontin, Horizant) recreationally, what dose do usually you take?	• Less than or equal to 900 mg • 901 to 1800 mg • 1801 to 3600 mg • Greater than 3600 mg
When you take quetiapine (Seroquel) recreationally, what dose do usually you take?	• Less than or equal to 100 mg • 100 to 199 mg • 200 to 399 mg • 400 to 799 mg • 800 to 1199 mg • Greater than 1200 mg
When you take olanzapine (Zyprexa) recreationally, what dose do usually you take?	• Less than or equal to 10 mg • 11 to 20 mg • 21 to 40 mg • Greater than 40 mg
When you take [insert drug] recreationally, what do you like about it? SELECT ALL THAT APPLY.	• Calms/relaxes me • Increases my sociability/reduces my inhibitions • Makes me feel euphoric • Improves my mood • Makes me feel numb • Helps me sleep • Gives me an 'out of body' experience • Helps me feel more empathetic • Other (please specify)

[a]Survey consent, question logic, instructions, and demographic/clinical items have been omitted from this table.

was conducted to assess patterns of use for each drug individually, focused on those reporting use for reasons other than a diagnosed medical condition, or for nontherapeutic purposes.

A complete-case logistic regression was used to identify factors associated with misuse of SGAs. Several demographic/clinical factors were incorporated as covariates, including age, gender, race/ethnicity, census region, income, marital status, employment status, educational status, insurance type, previous incarceration, previous SUD treatment and total attitudinal risk score. All analyses were reported using a significance level set at $P < .05$, and the regression model was reported using OR and 95% CI.

Results

A total of 1843 respondents were surveyed, including 1614 (87.6%) who reported never using an SGA, 145 (7.9%) who reported previously taking quetiapine, 59 (3.2%) who reported previously taking olanzapine, and 25 (1.4%) who reported previously taking both SGAs. Among the 229 respondents with a history of taking an SGA, 116 (50.7%; 95% CI: 44.0%, 57.3%) reported behaviors consistent with the study definition of misuse, while 113 (49.3%; 95% CI: 42.7%, 56.0%) did not. Demographic characteristics are available in Table 2. Respondents reporting misuse of either SGA were more likely to be male, employed, educated, to have a SUD diagnosis, and to have received SUD treatment

TABLE 2: Demographics and clinical characteristics of respondents[a]

		SGA use (n=229)		
	No SGA use (n=1614)[f] n (%)	No misuse (n=113) n (%)	Misuse (n=116) n (%)	*P* Value[g] n (%)
Age group, y				
18-24	255 (15.8)	14 (12.4)	14 (12.1)	.314
25-34	373 (23.1)	33 (29.2)	48 (41.4)	
35-44	386 (23.9)	35 (31.0)	33 (28.4)	
45-54	403 (25.0)	26 (23.0)	18 (15.5)	
55-59	197 (12.2)	5 (4.4)	3 (2.6)	
Gender				
Male	502 (31.1)	36 (31.9)	54 (46.6)	.026
Female	1107 (68.6)	76 (67.3)	62 (53.4)	
Nonbinary	5 (0.3)	1 (0.9)	0 (0.0)	
Race/Ethnicity[b]				
White/Caucasian	1021 (63.3)	84 (74.3)	68 (58.6)	.092
Black/African American	215 (13.3)	13 (11.5)	20 (17.2)	
Hispanic/Latino	270 (16.7)	11 (9.7)	20 (17.2)	
Other	108 (6.7)	5 (4.4)	8 (6.9)	
Census Region				
Northeast	272 (16.9)	22 (19.5)	29 (25.0)	.052
South	618 (38.3)	48 (42.5)	35 (30.2)	
Midwest	349 (21.6)	27 (23.9)	22 (19.0)	
West	375 (23.2)	16 (14.2)	30 (25.9)	
Income				
<$25,000	206 (12.8)	26 (23.0)	14 (12.1)	.003
$25,000-$49,999	542 (33.6)	43 (38.1)	33 (28.4)	
$50,000-$99,999	438 (27.1)	33 (29.2)	40 (34.5)	
≥$100,000	428 (26.5)	11 (9.7)	29 (25.0)	
Marital Status				
Single, Never Married	518 (32.1)	36 (31.9)	44 (37.9)	.048
Married	924 (57.2)	55 (48.7)	61 (52.6)	
Widowed	22 (1.4)	1 (0.9)	3 (2.6)	
Divorced/Separated	150 (9.3)	21 (18.6)	8 (6.9)	
Employed[c]	1062 (65.8)	63 (55.8)	99 (85.3)	<.0001
Educational Status, n (%)				
No Diploma	183 (11.3)	8 (7.1)	6 (5.2)	.001
High School/GED	488 (30.2)	49 (43.4)	30 (25.9)	
Some College	481 (29.8)	33 (29.2)	34 (29.3)	
College Degree	301 (18.6)	18 (15.9)	22 (19.0)	
Graduate Degree	161 (10.0)	5 (4.4)	24 (20.7)	
Insurance Type[d]				
Private	898 (55.6)	62 (54.9)	58 (50.0)	.438
Public	500 (31.0)	44 (38.9)	46 (39.7)	
Other	524 (32.5)	7 (6.2)	12 (10.3)	
Previous Incarceration	198 (12.3)	38 (33.6)	51 (44.0)	.109

TABLE 2: Demographics and clinical characteristics of respondents[a] (continued)

		SGA use (n=229)		
	No SGA use (n=1614)[f] n (%)	No misuse (n=113) n (%)	Misuse (n=116) n (%)	*P* Value[g] n (%)
Medical Comorbidities				
Anxiety	513 (31.8)	83 (73.5)	54 (46.6)	<.0001
Depression	472 (29.2)	79 (69.9)	60 (51.7)	.005
Bipolar Disorder	90 (5.6)	45 (39.8)	20 (17.2)	.0002
Schizophrenia	19 (1.2)	3 (2.7)	13 (11.2)	.011
PTSD	90 (5.6)	35 (31.0)	14 (12.1)	.0005
Chronic Pain	235 (14.6)	45 (39.8)	33 (28.4)	.069
Neuropathy	70 (4.3)	11 (9.7)	7 (6.0)	.298
Seizure Disorder	30 (1.9)	5 (4.4)	4 (3.4)	.704
Insomnia/Sleep Disorder	169 (10.5)	37 (32.7)	19 (16.4)	.004
Fibromyalgia	64 (4.0)	10 (8.8)	4 (3.4)	.088
SUD Diagnoses				
Opioids Only	43 (2.7)	11 (9.7)	20 (17.2)	<.0001
Alcohol Only	85 (5.3)	13 (11.5)	28 (24.1)	
Other Substances Only	25 (1.5)	6 (5.3)	7 (6.0)	
Poly-Substance	38 (2.4)	8 (7.1)	28 (24.1)	
None	1423 (88.2)	75 (66.4)	33 (28.4)	
Previous SUD Treatment	153 (9.5)	36 (31.9)	70 (60.3)	<.0001
Substance Use History				
Nicotine	912 (56.5)	80 (70.8)	101 (87.1)	.002
Cannabis	824 (51.1)	77 (68.1)	97 (84.3)	.004
Cocaine	295 (18.3)	38 (33.6)	74 (64.3)	<.0001
Ecstasy	169 (10.5)	26 (23.0)	66 (57.4)	<.0001
Methamphetamine	149 (9.2)	27 (23.9)	59 (51.3)	<.0001
Heroin	75 (4.6)	12 (10.6)	53 (46.1)	<.0001
Kratom	59 (3.7)	12 (10.6)	41 (35.7)	<.0001
Total Attitudinal Risk Score, Mean (SD)[e]	13.28 (5.46)	13.52 (5.08)	21.11 (6.02)	<.0001

SGA = second-generation antipsychotic.

[a]Note: columns may not add up to 100% given missing data or some categories where a respondent can choose multiple responses.

[b]'Other' includes those reporting Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or Other.

[c]'Employed' includes those reporting current employment or military status; excludes those reporting that they were not currently working, retired, or with student status.

[d]'Private' includes those with only private insurance, 'Public' includes those with Medicare or Medicaid, and 'Other' includes those only reporting use of a discount program/card, other, or no insurance coverage.

[e]Score (range 6-30) rendered from sum of 6 statements where higher scores indicate riskier knowledge, attitudes, and beliefs regarding medication/drug use.

[f]Targeted quotas employed by the sampling design included: Age (15% 18-24 years; 24% 25-34 years; 24% 35-44 years; 26% 45-54 years; 11% 55-59 years); Geographic region (37% South; 23% West; 22% Midwest; 18% Northeast); Race/ethnicity (63% Caucasian; 17% Hispanic; 13% African American; 5% Asian American; 2% other); Income (13% < $25,000; 36% $25,000-$49,999; 29% $50,000-$99,999; 22% $100,000+); and Education (13% some high school or less; 30% high school graduate; 29% some college; 18% college graduate; 10% graduate degree).

[g]Among individuals reporting SGA use, statistical comparison was performed comparing 'misuse and' 'no misuse' subgroups.

compared to those not reporting misuse. They were also more likely to indicate riskier medication-taking behaviors and comorbid psychiatric disorders, including anxiety, depression, bipolar disorder, schizophrenia, PTSD, and insomnia or a sleep disorder.

Within the total general population sample, the misuse prevalence of either quetiapine or olanzapine was estimated at 6.3% (n = 116/1843; 95% CI: 5.2%, 7.5%). The prevalence of obtaining either drug without a prescription was estimated at 4.0% (n = 74; 95% CI: 3.2%, 5.0%), including 2.9% (n = 53; 95% CI: 2.2%, 3.7%) for quetiapine and 1.4%

(n = 26; 95% CI: 0.9%, 2.1%) for olanzapine. The prevalence of using SGAs outside of medical guidance (either to treat symptoms or for reasons other than a diagnosed medical condition) was 5.9% (n = 109; 95% CI: 4.9%, 7.1%), including 3.9% (n = 72; 95% CI: 3.1%, 4.9%) for quetiapine and 2.7% (n = 50; 95% CI: 2.0%, 3.6%) for olanzapine.

Table 3 displays characteristics of SGA use, therapeutic misuse, and misuse for a nontherapeutic reason. Most respondents who reported having taken either SGA (70%-73%) did so to treat a diagnosed medical condition. However, approximately 1 in 5 respondents also detailed use for symptoms without their provider's knowledge, for nontherapeutic purposes, or for use with another drug/substance. Respondents indicating misuse identified several precipitating reasons, the most common (40%-46%) being that medications prescribed by their healthcare provider were not relieving their symptoms. This occurred relatively infrequently though, with less than half of respondents indicating their frequency of misuse to be regular (at least monthly). However, in instances where misuse was reported, coadministration of SGAs with other substances was relatively common. Respondents indicating misuse specifically for nontherapeutic purposes also frequently endorsed use with other substances, along with a variety of desirable effects observed, most frequently citing calming, euphoric, sociability, and sleep-related effects.

A total of 222 respondents with fully available data were included in the regression, with the full results available in Table 4. Overall, factors significantly associated with SGA misuse included being employed (OR = 4.64; 95% CI: 1.86%, 11.52), being previously treated for SUD (OR = 2.48; 95% CI: 1.08, 5.71), and having a higher attitudinal risk score regarding medications (OR = 1.23; 95% CI: 1.15, 1.33).

Discussion

In this study, the estimated prevalence of quetiapine and olanzapine misuse in adults aged 18 to 59 years was 6.3% based on data from a representative sample of US population. While approximately half of the respondents reporting previous use of quetiapine or olanzapine met criteria for misuse, it occurred infrequently (monthly or less). It was common for those who misused SGAs to have an additional SUD-related diagnosis. Similarly, it was found that SGAs were often misused in combination with other substances and those who reported misuse had higher attitudinal scores associated with riskier medication use.

This study provides valuable information regarding the extent of quetiapine and olanzapine misuse. While a growing number of studies evaluating the extent of SGA misuse have been published, little was known regarding their misuse prevalence in the general population, as much of the data is derived from sources with various limitations to estimating population-level estimates. For example, several studies have examined the issue using adverse event reporting system or poison control data.[11,18-21] While these are useful, they are often limited in demographic or outcomes data, likely underestimate the extent of the problem, and are biased toward events in which the person experiences an adverse drug event and subsequently seeks medical attention, and thus may overestimate the related patient harm. Other studies have assessed healthcare use[6,8,10] or postmortem toxicology data;[6,22] these select mainly patients experiencing harm associated with their misuse. Finally, studies have also estimated misuse within specific subpopulations, such as individuals with known use disorders,[3,4,23] individuals receiving psychiatric care in the hospital,[24] or incarcerated populations.[25] While such individuals are more likely to engage in SGA use, their sampling doesn't enhance understanding of the generalized scope of misuse. Accordingly, the present study sought to address some of these gaps in the present body of literature by providing one of the most generalizable estimates of quetiapine and olanzapine misuse published to date, and enhancing our understanding of why and how people misuse SGAs.

Several recent studies have also sought to compare the misuse of specific SGAs relative to each other. Quetiapine is consistently the most frequently cited among cases of misuse, though limited data also portend growing olanzapine misuse liability;[3,8,11,18,26,27] as a result, the present study chose to focus on these 2 SGAs specifically. A retrospective analysis using the US National Poison Data System identified quetiapine as the most misused antipsychotic from 2003 to 2013, accounting for 60.6% of antipsychotic-related misuse cases, followed by risperidone (15.2%) and olanzapine (7.0%).[18] Similarly, among people who misuse substances, a US-based survey identified quetiapine as the most misused SGA (90%), followed by olanzapine (28%).[3] A 2018 analysis of the European Medicines Agency (EMA) adverse event reporting system identified over 22 000 adverse drug reaction reports associated with misuse, abuse, dependence, or withdrawal of quetiapine and olanzapine from 2004 to 2016, with a higher proportional reporting ratio for quetiapine than olanzapine across each reporting category (1.01-5.25).[19] In a similarly designed analysis of the US FDA Adverse Event Reporting System (FAERS), among 4 SGAs studied (quetiapine, olanzapine, aripiprazole, and risperidone), quetiapine was the most commonly reported, followed by olanzapine.[12] Of the 27 962 reports of quetiapine-related adverse events, 3144 (11%) were misuse-related, compared to 1548 (8%) of the 19 228 olanzapine events. However, in the final 2 years of the study, the proportional reporting ratio of quetiapine and olanzapine were not significantly different, indicating a potential increase in olanzapine misuse. Using the World Health

TABLE 3: Patterns of use for quetiapine and olanzapine

Patients Indicating Use or Misuse	Quetiapine (n=170) n (%)	Olanzapine (n=84) n (%)
Primary Reason(s) for Use[a]		
To treat a diagnosed medical condition	124 (72.9)	59 (70.2)
To treat symptoms without my provider	35 (20.6)	31 (36.9)
For nontherapeutic purposes	40 (23.5)	29 (34.5)
To use with another drug to increase/enhance its effect	53 (31.2)	36 (42.8)
Patients Indicating Any Misuse (eg, therapeutic or nontherapeutic)	**Quetiapine (n=72) n (%)**	**Olanzapine (n=50) n (%)**
Reason(s) for Misuse[a]		
No longer able to obtain another medication they used to take	23 (31.9)	14 (28.0)
Medications prescribed by healthcare provider not relieving symptoms	29 (40.3)	23 (46.0)
Experiencing symptoms of withdrawal from SGA	19 (26.4)	19 (38.0)
Coping with symptoms of withdrawal from other drug/substance	21 (29.2)	11 (22.0)
Frequency of Misuse		
Once or twice in my life	33 (45.8)	11 (22.0)
Yearly	10 (13.9)	9 (18.0)
Monthly	12 (16.7)	13 (26.0)
Weekly	7 (9.7)	10 (20.0)
Daily	10 (13.9)	7 (14.0)
Coadministration With Other Substances[a]		
Opioids	46 (63.9)	24 (48.0)
Benzodiazepines	30 (41.7)	20 (40.0)
Alcohol	30 (41.7)	25 (50.0)
Other substances	1 (1.4)	1 (2.0)
Patients Indicating Misuse for Nontherapeutic Purposes	**Quetiapine (n=40) n (%)**	**Olanzapine (n=29) n (%)**
Coadministration With Other Substances[a]		
Opioids	21 (52.5)	23 (79.3)
Benzodiazepines	21 (52.5)	16 (55.2)
Alcohol	18 (45.0)	19 (65.5)
Other substances	1 (2.5)	0 (0.0)
What Respondent Likes About Use[a]		
Calms/relaxes	23 (57.5)	17 (58.6)
Improves sociability/ reduces inhibitions	15 (37.5)	14 (48.3)
Euphoria	18 (45.0)	18 (62.1)
Improves mood	13 (32.5)	13 (44.8)
Numbs	9 (22.5)	11 (37.9)
Helps with sleep	15 (37.5)	12 (41.4)
Out of body experience	7 (17.5)	8 (27.6)
Increases empathy	4 (10.0)	5 (55.6)
Other	2 (5.0)	0 (0.0)

SGA = second-generation antipsychotic.

[a]Indicates a 'select all that apply' item.

TABLE 4: Factors associated with SGA misuse

Variables	OR (95% CI)	*P* Value
Age group		
18-34 y	Reference	.302
35-59 y	0.65 (0.29, 1.47)	
Gender		
Female	Reference	.535
Male	0.63 (0.28, 1.42)	
Nonbinary	. . .	
Race/Ethnicity[a]		
White/Caucasian	Reference	.147
Black/African American	4.28 (1.19, 15.46)	
Hispanic/Latino	1.58 (0.50, 5.03)	
Other	2.39 (0.44, 12.87)	
Census Region		
Northeast	Reference	.116
Midwest	1.20 (0.36, 3.98)	
South	0.41 (0.15, 1.14)	
West	1.18 (0.35, 4.00)	
Income		
<$50,000	Reference	.616
≥$50,000	1.27 (0.49, 3.28)	
Marital Status		
Single/Never Married	Reference	.978
Married/Long-Term Partnership	1.07 (0.43, 2.67)	
Widowed/Divorced/Separated	1.13 (0.33, 3.82)	
Employed[b]	4.64 (1.86, 11.52)	.001
Educational Status		
Some School Up to Diploma/GED	Reference	.546
Some College	0.87 (0.35, 2.17)	
College/Graduate Degree	1.52 (0.54, 4.26)	
Insurance Type[c]		
Private	Reference	.100
Public	0.29 (0.08, 1.12)	
Other	0.20 (0.05, 0.87)	
Previous Incarceration	1.70 (0.71, 4.09)	.238
Treated for SUD	2.48 (1.08, 5.71)	.032
Total Attitudinal Risk Score[d]	1.23 (1.15, 1.33)	<.001

SGA = second-generation antipsychotic.

[a]'Other' includes those reporting Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or Other.

[b]'Employed' includes those reporting current employment or military status.

[c]'Private' includes those with only private insurance, 'Public' includes those with Medicare or Medicaid, and 'Other' includes those only reporting use of a discount program/card, other, or no insurance coverage.

[d]Score (range 6-30) rendered from sum of 6 statements where higher scores indicate riskier knowledge, attitudes, and beliefs regarding medication/drug use.

Organization VigiBase adverse event reporting system, Roy and colleagues similarly identified that quetiapine and olanzapine were implicated in the majority of SGA misuse reports.[26]

In the present study, lifetime quetiapine misuse was reported more frequently than olanzapine (3.9% vs 2.7%, respectively). However, given that more than twice as many respondents reported any use of quetiapine vs olanzapine, the relative availability and clinical use of quetiapine is likely one factor contributing to this difference. Several other factors may also explain the higher reporting of quetiapine misuse than other SGAs, including lower-cost generic availability, relative tolerability and side effect profile, increasing use for off-label indications, and differing pharmacologic activity at various receptors.[8,26] Further study is warranted to compare the relative misuse liability of the various SGAs and the rationale for differences observed.

Respondents reporting SGA misuse were more likely to also report an SUD diagnosis (related to opioids, alcohol, or multiple substances) and having received treatment for said diagnosis, a correlation that has also been observed in prior studies.[8,27] Several possible motivations for SGA misuse have been identified in the literature, including improving the *high* of other drugs, such as opioids;[28] helping come down from the *high* of other drugs;[8,29] achieving desirable sedative, hypnotic, calming, or hedonic effects from the SGA itself;[8,20] or alleviating untreated or undertreated psychiatric disorders.[28] Interestingly, there is also evidence indicating that quetiapine is effective as a treatment for cocaine use disorder or withdrawal symptoms associated with alcohol or opioid use disorders.[8] The present study seems to endorse these motivations, though it appears that misuse to treat an untreated or undertreated condition is the most common motivation.

Ultimately, the primary concern regarding misuse is whether it generates patient harm. While the present study did not assess this, poison control center data has identified the most common clinical effects associated with misuse as drowsiness/lethargy (both), tachycardia (both), slurred speech (both), agitation/irritability (olanzapine), and confusion (olanzapine).[18] Patients may also experience autonomic or psychologic withdrawal effects upon abrupt discontinuation.[8] Several reports have identified that SGA misuse is also associated with increased healthcare use and cost, and potential increased overdose mortality risk.[10,22] In Australia, researchers observed a 285-fold increase in quetiapine prescriptions over the 10-year period from 2006 to 2016, which corresponded with a 7.4-fold increase in quetiapine-related deaths in the same timeframe.[6] Data from the US Drug Abuse Warning Network (DAWN), a public health surveillance system for drug-related ED visits, identified a 90% increase in quetiapine-related ED visits

from 2005 to 2011, peaking at over 67 000 visits annually.[10] Over half of these visits were attributed to misuse, with the remaining related to suicide and adverse drug reactions. Across all antipsychotic-related ED visits, quetiapine was involved in approximately half, while olanzapine was identified in 9%. Furthermore, evidence from both the EMA and FAERS identified fatalities associated with SGA misuse reports, though these were typically polysubstance fatalities and neither study was designed to identify the cause of death.[11,19] Ultimately, there is not yet a compelling causative connection between SGA misuse and harm, but this remains an important area for future monitoring.

Though there is little definitive evidence of harm from SGA misuse, the risk is presumably greater in patients misusing them more frequently or with other substances. In the present study, patients misusing quetiapine or olanzapine were more likely to endorse more risky behaviors regarding prescription drugs. The 6-item survey used to assess attitudinal risk towards medication misuse has been shown to be correlated to gabapentin and pregabalin misuse as well.[12] To this extent, a majority of respondents misusing quetiapine or olanzapine in the present study reported use with other CNS depressants, such as opioids, benzodiazepines, or alcohol. Furthermore, patients reporting SGA misuse were also more likely to report previous use of a number of other substances with misuse potential (eg, cannabis, cocaine, ecstasy, methamphetamine, heroin, nicotine, and kratom). This pattern is in line with previous studies that have also identified SGA misuse commonly occurring in conjunction with other substances, such as opioids, anxiolytics, sedatives, antidepressants, or stimulants.[8,10,23,28,30] Despite the tendency to misuse in conjunction with other CNS depressants, in the present study, most participants reported misuse no more frequently than monthly; this infrequent misuse pattern of quetiapine specifically has been previously reported among a sample of persons who regularly inject drugs.[30]

Limitations

There are several limitations of the current study worth noting. As with most surveys, there is potential for self-report or recall bias. To minimize this, the survey was anonymous, participation was voluntary, and questions about SGA misuse only propagated if there was an initial indication of any SGA use. Though participants were compensated for their time, there was no requirement for previous SGA use to participate. Furthermore, non-SGA questions were incorporated into the survey and participants were asked to confirm answers were selected truthfully within the survey. The external validity of this study may be limited because of its sample size, and results may not be relevant across all populations. Finally, the questionnaire only focused on olanzapine and quetiapine; further work with other SGAs would be useful as the results cannot be extrapolated across the class.

Conclusion

In this sample of US adults, the lifetime prevalence of quetiapine or olanzapine misuse was identified at 6.3%. This misuse occurred on an infrequent basis, primarily among persons with other SUDs, and was most commonly the result of under-treatment of existing medical conditions.

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