5-1-2019

Comparison of Quetiapine Abuse and Misuse Reports to the FDA Adverse Event Reporting System With Other Second-Generation Antipsychotics

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Publication Info

Published in *Substance Abuse: Research and Treatment*, Volume 13, 2019.

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Substance Abuse: Research and Treatment
Volume 13: 1–8

DOI: 10.1177/1178221819844205
SAGE

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ABSTRACT

BACKGROUND: Second-generation antipsychotics (SGAs) are assumed to have little abuse potential. However, reports of quetiapine abuse have emerged as prescribing has increased in recent years. The US Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) provides postmarketing information regarding adverse drug events (ADEs). This is the first study to analyze quetiapine abuse-related ADEs reported to FAERS to determine whether a disproportionate rate of such events have been reported when compared with other commonly used SGAs.

METHODS: A cross-sectional analysis of FAERS data from January 1, 2015, to December 31, 2017, was performed. The total number of all-cause and abuse-related ADEs reported to FAERS regarding quetiapine, olanzapine, aripiprazole, and risperidone were identified, along with demographic and mortality data. The proportional reporting ratio (PRR) was calculated to assess disproportionate reporting of abuse-related adverse drug reactions between quetiapine and each of three alternative SGA medications.

RESULTS: Abuse-related ADEs represented 11% (3144/27 962) of total ADEs reported for quetiapine, 8% for olanzapine (1548/19 228), 5% (1380/29 699) for aripiprazole, and 3% (1168/45 518) for risperidone. The PRRs (95% confidence interval) for quetiapine versus olanzapine, aripiprazole, and risperidone were 1.40 (1.32-1.48), 2.42 (2.28-2.57), and 4.38 (4.10-4.68), respectively, indicating that abuse-related events were significantly more likely to be reported with quetiapine than each comparator drug. In addition, more deaths were reported among the abuse-related events regarding quetiapine (673) than olanzapine (200), aripiprazole (88), and risperidone (143).

CONCLUSION: This study corroborates recent evidence indicating that quetiapine might possess a significantly higher abuse potential than other commonly used SGAs. Although prospective studies are needed to better understand the abuse potential of quetiapine, increased vigilance in monitoring for signs of substance abuse might be warranted when prescribing quetiapine.

KEYWORDS: quetiapine, olanzapine, risperidone, aripiprazole, prescription drug abuse, FAERS, adverse event reporting system, second-generation antipsychotics

RECEIVED: February 4, 2019. **ACCEPTED:** February 7, 2019.

TYPE: Original Research

FUNDING: Dr Frei was supported, in part, by a NIH Clinical and Translational Science Award (National Center for Advancing Translational Sciences, UL1 TR001120, UL1 TR002645, and TL1 TR002647) while the study was being conducted. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, the National Institutes of Health, or the authors' affiliated institutions.

DECLARATION OF CONFLICTING INTERESTS: Dr Frei has received research grants, to his institution, for investigator-initiated cancer and infectious diseases research, from Allergan (formerly Forest), AstraZeneca, Bristol Myers Squibb, and Pharmacyclics, in the past 3 years. The additional authors declare no conflicts of interest.

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Introduction

Quetiapine (Seroquel), olanzapine (Zyprexa), risperidone (Risperdal), and aripiprazole (Abilify) belong to a class of medications known as second-generation antipsychotics (SGAs).[1] Quetiapine is US Food and Drug Administration (FDA)-approved to treat schizophrenia and bipolar disorder and as an adjunct agent for major depressive disorder. However, it is also increasingly being used for off-label indications such as insomnia and anxiety.[1–3] Its antipsychotic activity is believed to be mediated through dopamine D_2 and serotonin 5-HT_2 antagonism, though it also functions as an antagonist at other brain receptors, including serotonin 5-HT_{1a}, dopamine D_1, histamine H_1, and adrenergic alpha$_1$ and alpha$_2$.[1] Olanzapine, risperidone, and aripiprazole are believed to have similar mechanisms of action: antagonism of serotonin 5-HT_2 and dopamine D_2 receptors, though the level of activity at these receptors differs to some extent between drugs.

Though not classified as controlled substances or typically thought of as drugs of abuse, recent evidence suggests an emerging abuse liability of SGAs, particularly quetiapine.[2–4] The mechanism behind this abuse potential and rationale as to why quetiapine has shown higher rates of abuse is unclear. Some theories have attributed quetiapine abuse to the drug's effects on the dopamine reward system, particularly in the

nucleus accumbens, though this has not been definitively proven.[2,5–7] Physiologic mechanisms aside, individuals who use SGAs illicitly have reported that abuse/misuse can induce hallucinogenic effects, numbness, and euphoria; desirable sensations for many with substance use disorders.[6] Alternatively, others point to it as being used predominantly for its sedative or anxiolytic properties to self-medicate various symptoms such as anxiety, insomnia, or drug withdrawal or to enhance or modify the effects of other psychoactive drugs.[2,5,7,8] Relatively, benign central nervous system (drowsiness, slurred speech, agitation, etc) and cardiovascular (tachycardia, hypotension, syncope, electrocardiography changes, etc) symptoms are the most commonly reported adverse effects observed with quetiapine abuse, though more serious consequences, including fatalities, have been reported.[3,4,9]

Quetiapine abuse reports began to emerge in the early 2000s, but initially were limited to case reports and were most commonly observed in the prison population.[7,8] However, recently, several retrospective studies of American and Australian poison control center data have provided significantly more data on the problem.[3,4,9] In addition, a 2018 analysis of the European Medicines Agency (EMA) Adverse Event Reporting System (AERS) identified 18 112 and 4178 adverse drug event (ADE) reports pertaining to misuse, abuse, dependence, or withdrawal of quetiapine and olanzapine, respectively.[2] This represented 9% of 209 571 total quetiapine ADE reports and 8% of 55 100 total olanzapine ADE reports over the same timeframe. This study raised concern for growing abuse of these medications and demonstrated a significantly higher likelihood with quetiapine than olanzapine (though it is questionable whether this 1% difference represents an increased abuse liability that is meaningful clinically). Although these data are alarming, it is unclear whether the findings in the EMA database are generalizable within the United States. Furthermore, data comparing the abuse potential of quetiapine with other commonly prescribed SGAs are currently limited.

Therefore, the current study was conducted to quantify abuse-related events of quetiapine, olanzapine, aripiprazole, and risperidone reported to the US FDA Adverse Event Reporting System (FAERS) to compare quetiapine abuse reporting with other commonly used SGAs within a US cohort.

Methods

Data source

FAERS serves as a pharmacovigilance tool utilized to identify concerning postmarketing medication safety trends.[10] FAERS is a passive surveillance system, relying on voluntary ADE reports from healthcare professionals or consumers and mandatory reports from pharmaceutical companies. FAERS data are publicly available through the FDA.

For this study, FAERS Quarterly Data Files from the first quarter of 2015 (2015 Q1) through the fourth quarter of 2017 (2017 Q4) were downloaded from the FDA Web site. Because some ADE reports were submitted with an initial report and several follow-up reports in the same "CASEID", duplicate reports were removed, with the most recent version included in the study.

Query structure

Queries were designed to extract data for each drug of interest in FAERS using brand and generic names listed in the Drugs@FDA Database.[11] Reports of a broad definition of abuse-related ADEs (collectively referred to as "abuse-related events" from here forward) were generated from FAERS using the following search terms: "drug abuse," "drug abuser," "drug dependence," "intentional product misuse," "intentional product use issue," "polysubstance dependence," "substance abuse," "substance abuser," "drug withdrawal syndrome," "intentional overdose," "maternal use of illicit drugs," "multiple drug overdose intentional," "addiction," "drug addiction," "dependence," "tolerance increased," "intoxication," "overdose," "pathological inebriation," "drug diversion," "euphoric mood," "polysubstance abuse," and "drug use via unapproved administration route." This collection of terms was based on previously published assessments that utilized AERS data to identify substance abuse-related events.[12] Though demographic data available in the database are limited, age and sex were captured for each case to assess for possible differences with regard to likelihood of abuse.

Because it is possible that overdose-related events may or may not occur as a result of intentional misuse or abuse, we also conducted a secondary analysis with the terms "intentional overdose" and "overdose" removed, with all other terms from the original search query remaining. These events are collectively referred to as "non-overdose abuse-related events" from here forward.

Data analysis

The proportional reporting ratio (PRR) is a pharmacovigilance tool utilized to identify disproportional reporting of specific adverse events from one drug versus another.[13] PRRs and their 95% confidence intervals (CI) were calculated using the equations $PRR = (Q^a/Q^t)/(C^a/C^t)$ and 95% $CI = e^{(\ln(PRR) \pm 1.96 \times \sqrt{(1/Q^a - 1/Q^t + 1/C^a - 1/C^t)})}$, where Q^a represents the number of abuse-related quetiapine ADEs, Q^t represents the total number of quetiapine ADEs, C^a represents the number of abuse-related ADEs for the comparator medication (in this case olanzapine OR aripiprazole OR risperidone), and C^t represents the total number of ADEs for the comparator medication.[14,15] For example, if there were 100 total quetiapine ADEs with 20 related to abuse and 100 total olanzapine ADEs with 10 related to abuse, the following equation would be utilized: $PRR = (20/100)/(10/100) = 2$, indicating that quetiapine had a stronger association with abuse-related events than olanzapine.

Table 1. Patient Demographics.

CHARACTERISTIC	QUETIAPINE	OLANZAPINE	ARIPIPRAZOLE	RISPERIDONE
Median patient age (IQR)—all-cause events	51 (35-65)	47 (32-61)	40 (26-55)	35 (17-55)
Median patient age (IQR)—abuse-related events	44 (31-55)	41 (30-55)	37 (25-50)	40 (22-52)
Median patient age (IQR)—non-overdose abuse-related events	46 (32-56)	42 (30-57)	40 (25-54)	41 (22-53)
Percent male—all-cause events	42	51	41	80
Percent male—abuse-related events	43	48	40	61
Percent male—non-overdose abuse-related events	41	44	38	64

Data analysis was performed using Microsoft Access 2016 (Microsoft Corporation, Redmond, WA), Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), and JMP Pro 13.2.1 (SAS Institute, Cary, NC). Odds ratios and their 95% CIs were calculated to compare mortality rates between drugs. Two-sided *P* values were utilized. Alpha values less than 0.05 were considered to be significant.

This study was deemed exempt from institutional review board (IRB) review by the University of Texas Health San Antonio IRB committee (HSC20180629N).

Results

A total of 112 138 ADEs related to quetiapine, olanzapine, aripiprazole, and risperidone were reported to FAERS during the period of January 1, 2015, to December 31, 2017 (some patients were on more than one of these medications so this total does not equal the summation of event reports from each individual medication). From this total, 6603 (6%) reports were abuse-related. The median ages of all reports for each individual drug varied from 35 to 51 years of age. With the exception of risperidone, in which males were more commonly reported in terms of all-cause and abuse-related reports, females accounted for a slightly higher proportion of all-cause and abuse-related events for each medication.

Quetiapine ADEs

A total of 27 962 all-cause quetiapine ADEs were reported, of which 3144 (11%) reports were abuse-related. The median patient age among abuse-related event reports was 44 years (interquartile range [IQR] = 31-55), and females represented a slightly higher proportion of these events (57%) (Table 1). Table 2 displays the annual rate of abuse-related reports identified. Over the course of the study, the proportion of abuse-related events reported to FAERS changed little from year to year. The five most common abuse-related terms reported were drug abuse (29%), overdose (26%), intentional overdose (17%), intentional product misuse (17%), and drug withdrawal syndrome (9%) (Table 3). Among the patients with an abuse-related event, 673 deaths (21%) were reported (Table 3).

Among the 3144 abuse-related events, non-overdose abuse-related events accounted for 1926 reports (61%). In this cohort of patients with non-overdose abuse-related events, the median patient age was 46 years (IQR = 32-56), 59% were female, and 396 (21%) fatalities were reported.

Olanzapine ADEs

A total of 19 228 all-cause olanzapine ADEs were reported, of which 1548 (8%) reports were abuse-related. The median patient age among abuse-related event reports was 41 years (IQR = 30-55), with females representing 52% of reports (Table 1). The five most commonly reported abuse-related terms were overdose (40%), intentional overdose (21%), drug abuse (21%), intentional product misuse (9%), and drug withdrawal syndrome (7%) (Table 3). Among the patients with an abuse-related event, 200 deaths (13%) were reported (Table 3).

Among the 1548 abuse-related events, non-overdose abuse-related events accounted for 675 reports (44%). In this cohort of patients with non-overdose abuse-related events, the median patient age was 42 years (IQR = 30-57), 56% were female, and 90 (13%) fatalities were reported.

Aripiprazole ADEs

A total of 29 699 all-cause aripiprazole ADEs were reported, of which 1380 (5%) reports were abuse-related. The median patient age among abuse-related event reports was 37 years (IQR = 25-50), with females representing 60% of the reports (Table 1). The five most common abuse-related terms reported were intentional overdose (33%), overdose (25%), drug withdrawal syndrome (12%), drug abuse (11%), and intentional product misuse (9%) (Table 3). Among the patients with an abuse-related event, 88 deaths (6%) were reported (Table 3).

Among the 1380 abuse-related events, non-overdose abuse-related events accounted for 630 reports (46%). In this cohort of patients with non-overdose abuse-related events, the median patient age was 40 years (IQR = 25-54), 62% were female, and 17 (3%) fatalities were reported.

Risperidone ADEs

A total of 45 518 all-cause risperidone ADEs were reported, of which 1168 (3%) reports were abuse-related. The median

Table 2. Annual Abuse-Related Events Reported For Quetiapine, Olanzapine, Aripiprazole, and Risperidone and Proportional Reporting Ratios (PRRs).

	2015	2016	2017	YEARS COMBINED
Annual numbers of events				
Quetiapine				
Abuse-related event reports/Total events reported (%)	1131/8526 (13)	900/8567 (11)	1113/10869 (10)	3144/27962 (11)
Olanzapine				
Abuse-related event reports/Total events reported (%)	582/9094 (6)	428/4468 (10)	538/5666 (10)	1548/19228 (8)
Aripiprazole				
Abuse-related event reports/Total events reported (%)	285/7320 (4)	356/8418 (4)	739/13961 (5)	1380/29699 (5)
Risperidone				
Abuse-related event reports/Total events reported (%)	333/11729 (3)	397/10724 (4)	438/23065 (2)	1168/45518 (3)
PRRs				
Quetiapine vs Olanzapine				
PRR of abuse-related events (95% CI)	2.07 (1.88-2.28)	1.10 (0.98-1.22)	1.08 (0.98-1.19)	1.40 (1.32-1.48)
PRR of non-overdose abuse-related events (95% CI)	2.57 (2.27-2.91)	1.69 (1.43-2.00)	1.73 (1.47-2.04)	1.96 (1.80-2.14)
Quetiapine vs Aripiprazole				
PRR of abuse-related events (95% CI)	3.41 (3.00-3.86)	2.48 (2.21-2.80)	1.93 (1.77-2.12)	2.42 (2.28-2.57)
PRR of non-overdose abuse-related events (95% CI)	3.67 (3.14-4.29)	2.67 (2.27-3.13)	3.08 (2.66-3.57)	3.25 (2.97-3.55)
Quetiapine vs Risperidone				
PRR of abuse-related events (95% CI)	4.67 (4.15-5.26)	2.84 (2.53-3.18)	5.39 (4.84-6.01)	4.38 (4.10-4.68)
PRR of non-overdose abuse-related events (95% CI)	6.29 (5.35-7.39)	3.54 (3.01-4.17)	7.47 (6.30-8.86)	5.89 (5.36-6.48)

patient age among abuse-related event reports was 40 years (IQR = 22-52), with 39% of reports occurring in females (Table 1). The five most common abuse-related terms reported were overdose (32%), intentional overdose (27%), intentional product misuse (13%), drug abuse (11%), and drug withdrawal syndrome (9%) (Table 3). Among the patients with an abuse-related event, 143 deaths (12%) were reported (Table 3).

Among the 1168 abuse-related events, non-overdose abuse-related events accounted for 532 reports (46%). In this cohort of patients with non-overdose abuse-related events, the median patient age was 41 years (IQR = 22-53), 36% were female, and 41 (8%) fatalities were reported.

Comparison of SGAs and PRRs

The PRRs (95% CI) for quetiapine versus olanzapine, aripiprazole, and risperidone were 1.40 (1.32-1.48), 2.42 (2.28-2.57), and 4.38 (4.10-4.68), respectively, indicating that abuse-related events were significantly more likely to be reported with quetiapine than each of the comparator drugs. However, during the final 2 years of the study, the PRR (95% CI) of quetiapine compared with olanzapine was not statistically significantly higher (1.10 [0.98-1.22] and 1.08 [0.98-1.19], respectively). When comparing mortality rates associated with abuse-related events, fatalities were reported in a higher proportion of quetiapine events than olanzapine (abuse-related: 22% vs 13%, odds ratio = 1.93 [95% CI = 1.61-2.31]; non-overdose abuse-related: 21% vs 14%, odds ratio = 1.64 [95% CI = 1.27-2.12]; patients on both quetiapine and olanzapine were excluded from this analysis).

In the secondary analysis excluding overdose events, the PRRs (95% CI) for non-overdose abuse-related events for quetiapine versus olanzapine, aripiprazole, and risperidone were 1.96 (1.80-2.14), 3.25 (2.97-3.55), and 5.89 (5.36-6.48), respectively.

In comparing the PRR (95% CI) of abuse-related events of the other medications analyzed (ie, olanzapine vs aripiprazole, olanzapine vs risperidone, and aripiprazole vs risperidone), events were significantly less likely to be reported with both aripiprazole (0.58 [0.54-0.67]) and risperidone (0.32 [0.3-0.34]) than olanzapine, while risperidone was also significantly less likely to be reported than aripiprazole (0.55 [0.51-0.60]).

Table 3. Abuse-Related Events Reported For Quetiapine, Olanzapine, Aripiprazole, and Risperidone.

REPORTED EVENT[A]	QUETIAPINE EVENTS, N (%)	OLANZAPINE EVENTS, N (%)	ARIPIPRAZOLE EVENTS, N (%)	RISPERIDONE EVENTS, N (%)
Drug abuse	895 (29)	324 (21)	147 (11)	133 (11)
Overdose	823 (26)	626 (40)	346 (25)	377 (32)
Intentional overdose	545 (17)	331 (21)	454 (33)	320 (27)
Intentional product misuse	544 (17)	140 (9)	118 (8)	155 (13)
Drug withdrawal syndrome	274 (9)	112 (7)	162 (12)	100 (9)
Intentional product use issue	146 (5)	37 (2)	66 (5)	42 (4)
Drug dependence	127 (4)	37 (2)	47 (3)	46 (4)
Euphoric mood	52 (2)	33 (2)	43 (3)	25 (2)
Substance abuse	35 (1)	6 (0.4)	38 (3)	29 (3)
Dependence	19 (0.6)	10 (0.6)	28 (2.0)	19 (1.6)
Drug diversion	18 (0.6)	5 (0.3)	4 (0.3)	22 (1.9)
Drug abuser	2 (0.1)	2 (0.1)	5 (0.4)	3 (0.3)
Total global events reported to FAERS	27962	19228	29699	45518
Total abuse-related events (% of total events)	3144 (11%)	1548 (8%)	1380 (5%)	1168 (3%)
Total non-overdose abuse-related events	1926	675	630	532
Deaths among abuse-related events	673	200	88	143
Deaths among non-overdose abuse-related events	396	90	17	41
Deaths among overdose abuse-related events	277	110	71	102

[a]Multiple reactions might be listed for a specific case.

Discussion

In the present study, we examined spontaneously reported quetiapine abuse and compare its likelihood to that of other commonly used SGAs through analysis of ADEs reported to FAERS from 2015 to 2017. To the best of our knowledge, this is the first study to utilize FAERS to compare quetiapine abuse/misuse with other SGAs in the United States and the first to utilize AERS data to compare quetiapine with risperidone or aripiprazole in addition to olanzapine. These FAERS data provide further corroboration that quetiapine might possess a greater abuse liability than other SGAs. The primary outcome of the present study, PRR, indicated that abuse-related events were significantly more commonly reported with quetiapine than olanzapine (1.40, 95% CI = 1.32-1.48), aripiprazole (4.38, 95% CI = 4.10-4.68), and risperidone (2.42, 95% CI = 2.28-2.57). Though quetiapine is the most commonly prescribed SGA in the United States,[16] this study indicates that the greater number of abuse-related events reported for quetiapine is not simply a result of greater use of quetiapine, as the PRR compares the likelihood of abuse-related events as a proportion of total events reported for that specific drug. Interestingly, though, olanzapine also showed significantly higher PRRs for abuse-related events than the other comparator SGAs (PRR [95% CI] of aripiprazole vs olanzapine = 0.58 [0.54-0.67] and risperidone vs olanzapine = 0.32 [0.3-0.34]), and the PRR for quetiapine versus olanzapine was only significantly higher during the first of the three years of this study. These data indicate that olanzapine might also have a greater abuse liability than other SGAs.

Previous data regarding quetiapine abuse are limited and have primarily been drawn from case reports and recent retrospective analyses of poison control data, emergency department (ED) utilization, and the EMA's AERS.[2–4,7–9] Among the first studies examining the abuse potential of quetiapine was an analysis of the Drug Abuse Warning Network (DAWN), a US healthcare surveillance system that estimates drug-related ED visits nationally.[8] This study identified significantly more reports of abuse-related events with quetiapine than other antipsychotics. From 2005 to 2011, quetiapine was responsible for, on average, 27114 misuse/abuse-related ED visits annually, significantly more than clozapine (608, $P < .001$), olanzapine (4528, $P < .001$), and risperidone (5804, $P < .001$). Misuse/abuse events were the most common reason for quetiapine-related ED visits over that time, and quetiapine-related misuse/abuse events accounted for 52% of the total misuse/abuse events reported for all antipsychotics over that period (n = 52635).

However, quetiapine was responsible for only 35% of total ED visits related to a SGA-induced adverse reaction. Thus, abuse-related presentations for quetiapine were higher than expected relative to other antipsychotics given the proportion of overall ADE presentations. This analysis also identified a 90% increase in quetiapine-related ED visits from 2005 to 2011, including a 67% increase in visits specifically relating to quetiapine misuse or abuse ($P = .06$). Though this did not reach statistical significance, these data might indicate an increasing trend of quetiapine misuse/abuse over that period. Furthermore, the DAWN data reported that quetiapine is infrequently abused alone, as only 25% of the misuse/abuse events did not involve another drug. Sedatives/anxiolytics (46%), benzodiazepines (38%), antidepressants (33%), alcohol (27%), and nonalcohol illicits (22%) were identified in greater than 20% of quetiapine misuse/abuse cases. However, as not all instances of quetiapine misuse/abuse result in ED visits, this methodology alone does not provide an all-encompassing look at the issue.

Three recent studies utilizing poison control center data similarly identified a significant abuse potential of quetiapine.[3,4,9] Klein et al[3] identified a total of 3497 single-substance SGA-abuse-related events reported to the American Association of Poison Control Centers National Poison Data System (NPDS) from 2003 to 2013, of which 60.6% (n = 2118) involved quetiapine. The next most frequently reported SGAs were risperidone (15%, n = 530) and olanzapine (7%, n = 246). In this study, only 2% and 0.1% of the 1446 reports of quetiapine abuse for which medical outcomes data were available resulted in major outcomes or mortality, respectively. Klein-Schwartz et al[9] focused specifically on quetiapine misuse or abuse and related toxicity, identifying 3116 cases reported to the NPDS from 2005 to 2011, with moderate to major adverse effects occurring in 25% of cases ("moderate" was defined as pronounced, prolonged, systemic effects where treatment is usually indicated, whereas "major" was defined as life-threatening effects). More than 75% of these cases were treated in the ED and/or required medical admission, though no fatalities were reported. A third study assessed quetiapine misuse utilizing poison control center data from Victoria, Australia, but did not compare these data with other SGAs, identifying a 6-fold increase in quetiapine-related overdoses and misuse events reported from 2006 to 2016, as well as a 7-fold increase in quetiapine-related deaths.[4] There was a significant positive correlation between both the increased overdose ($r = 0.75$, $P < .001$) and mortality ($r = 0.82$, $P < .01$) rates and the increase in quetiapine prescribing over this period. By the final year of the study, quetiapine had become the fifth most common drug exposure reported to the Victoria poison control center. Similar to the results observed by Klein et al,[3] this study indicated that quetiapine was commonly misused alongside other drugs. Antidepressants (42%) and benzodiazepines (40%) were the most commonly reported concomitant drugs ingested in quetiapine overdoses.[4]

In a 2018 study using similar methodology to the present assessment reported in this article, Chiappini and Schifano[2] analyzed quetiapine ADEs related to abuse, misuse, dependence, or withdrawal reported to the EMA AERS from 2004 to 2016 in comparison with olanzapine. Chiappini et al identified 18 112 quetiapine abuse/misuse/dependence/withdrawal events (9% of 209 571 total quetiapine ADEs) versus 4178 such ADEs with olanzapine (8% of 55 100 total olanzapine ADEs). The available data did not demonstrate a consistently increasing trend in the number of abuse-related reports annually. However, the 4 years with the most reports occurred from 2009 to 2012, with less events reported in more recent years. In this study of the EMA AERS, PRRs were calculated separately for misuse/abuse, dependence, and withdrawal-related adverse drug reaction (1.07, 1.01, and 5.25, respectively, for quetiapine vs olanzapine). Among the abuse-related events reported, 368 (45%) fatalities were identified relating to quetiapine versus 79 (35%) fatalities in the olanzapine group.

Similar to the EMA AERS data, within FAERS, "drug abuse" was the most commonly identified abuse-related ADE identified. However, in our study, the next most commonly identified ADEs were overdose and intentional overdose, whereas Chiappini and colleagues did not include overdose events in their analysis.[2] Although overdose might occur as a result of drug abuse or misuse, there are alternative factors that might lead to drug overdose (eg, suicide attempt, misunderstanding of how to take the medication, concomitant use of interacting drugs, etc). To account for this potential confounder, a secondary analysis utilized a modified PRR that excluded overdose events from the composite measure of abuse-related adverse event. This secondary analysis revealed an even larger PRR and stronger association of quetiapine with drug abuse/misuse when compared with the other three SGAs. The PRRs of quetiapine versus olanzapine, risperidone, and aripiprazole were 1.96 (95% CI = 1.80-2.14), 5.89 (95% CI = 5.36-6.50), and 3.25 (95% CI = 2.97-3.55), respectively, when overdose events were excluded. Given that Chiappini and colleagues did not include overdose events in their analysis, this secondary cohort provides a more similar comparison with the EMA data, which displayed an overall PRR for all abuse-related events of 1.13 when comparing quetiapine to olanzapine.[2]

Within the FAERS data, quetiapine abuse-related events were most commonly reported in middle-aged females (median 44 years [31-55]; 57% female). Data from previous studies have been inconsistent with regard to such demographic data. Although the DAWN[8] and Australian poison control center analyses[4] similarly identified higher proportions of females (57% and 68%, respectively), the EMA AERS data[2] displayed little difference with regard to sex among the quetiapine abuse-related events, with a female/male ratio of 0.96. In both US poison control center studies, the median age was lower (17 years, IQR = 15-27 years and 23 years, range = 4-89 years, respectively, in the studies by Klein et al[3] and Klein-Schwartz

et al[9]) and males were reported more commonly (62% of total quetiapine abuse/misuse reports and 1.7 male/female ratio in abuse reports in the 2 studies, respectively). The reasons for these differences are unknown, but might be a result of different reporting sources among the various databases.

Though the DAWN[8] and Australian poison control center[4] studies identified significant increases in annual quetiapine abuse-related events in more recent years, our study did not identify a significant trend in the number of reports annually. This might be due to several factors, including the shorter and more recent study period utilized. However, similar to our findings, the EMA AERS data similarly failed to demonstrate a consistently increasing trend in quetiapine-related ADEs reported annually and actually reported somewhat lower numbers of events in the most recent years, after a peak in 2012.[2]

Poison control center data have indicated that serious toxicity is possible, but overall very few quetiapine abuse-related events resulted in fatalities, possibly because the patients in these studies received timely help, or because these studies did not capture fatalities that occurred outside the hospital.[3,4,9] The US poison control center studies included only cases in which quetiapine was ingested as a single-drug event. Klein et al[3] reported that only 0.1% of quetiapine abuse cases resulted in death, whereas Klein-Schwartz et al[9] did not identify any fatalities. In Victoria, Australia, Lee et al[4] identified 1066 fatalities examined by the local coroner in which quetiapine was present during postmortem toxicology reports. Among these cases, however, quetiapine toxicity was determined to be the sole cause of death in only 13 (1.2%) cases. In both the present study of FAERS, as well as the analysis of EMA AERS data, a number of deaths were reported (673 and 368 fatalities, respectively) among the quetiapine abuse reports.[2] Furthermore, in our study the percentage of deaths reported among quetiapine abuse-related events (n = 673; 21%) was much higher than that of olanzapine (n = 200; 12.9%), aripiprazole (n = 88; 6.4%), and risperidone (n = 143; 12.2%), which raises further concern regarding quetiapine abuse. However, it is important to note that many potential confounders exist in utilizing FAERS data for this purpose, particularly that the cause of death is not reported in FAERS. The available data simply state when fatalities occur but do not indicate whether death was directly related to the specific drug or whether concomitant drugs might have also played a role. Furthermore, reporting bias might play a role as well, as abuse cases with negative outcomes are likely more often identified and reported to the FDA.

Previous studies of DAWN and poison control center data compared quetiapine with a number of SGAs, both identifying risperidone to be the second most commonly reported SGA in terms of abuse/misuse-related events.[3,8] However, the EMA AERS analysis only compared quetiapine with olanzapine.[2] Our study also included two additional commonly used SGAs, aripiprazole and risperidone, in addition to olanzapine, thus providing additional insight. Although abuse reports were significantly more common with quetiapine than all 3 comparator drugs, the PRRs were significantly higher when comparing quetiapine with aripiprazole (2.42 [95% CI = 2.28-2.57]) and risperidone (4.38 [95% CI = 4.10-4.68]) than olanzapine (1.40 [95% CI = 1.32-1.48]), indicating risperidone was the least likely to be abused. In fact, risperidone had the greatest number of total ADEs reported to FAERS of the 4 comparator drugs but the lowest number of abuse-related events.

Limitations

FAERS data have several limitations. One such limitation is an inability to accurately identify concomitant drug use. Assessments of both the DAWN and EMA AERS databases indicate quetiapine abuse-related events frequently include multiple drugs.[2,8] In fact, 75% of misuse/abuse events identified in the DAWN database included coingestion of at least one other medication.[8] Among the abuse-related events reported to the EMA AERS, opioids and benzodiazepines were among the drug classes most commonly used with quetiapine, while the DAWN data also point toward alcohol, antidepressants, anxiolytics/sedatives/hypnotics, and illicit drugs as common concomitant drugs in quetiapine abuse-related events.[2,8] In particular, this inability to identify concomitant drug use limits our ability to accurately assess whether the drug in question was responsible for fatalities reported. In addition to concomitant drug use, there is only limited information regarding patient demographics, clinical outcomes, or drug doses, which reduces the ability to control for potential confounders. The reasons for the differences observed in the EMA data and FAERS data are likely multifactorial, and the data available from this study do not provide any firm basis to prove why these differences are present. Possible reasons might include cultural issues or decreasing reporting trends due to normalization of abuse.

Furthermore, FAERS data are based on spontaneous reports, and the FDA does not require an established causal relationship prior to event reporting. This presents a number of potential limitations. First, there is no certainty that the medication in question was primarily responsible for the reported event. It also means that the same event might be reported multiple times. In addition, given the spontaneous reporting structure, these data cannot be used to measure incidence of the event in question. Despite the fact that our list of search terms was guided by several previous studies, it is possible that not all drug abuse events reported were captured. There is also a potential for reporting bias, with reporting possibly influenced by outside factors such as media coverage or knowledge of previous studies identifying an abuse liability with quetiapine, as well as increased likelihood of events with more severe outcomes being reported.

Beyond FAERS-specific limitations, differing national prescribing trends in the United States compared with Europe or

Australia might explain some differences between the FAERS data and the trends observed in previous studies, though the direct impact of these differences cannot be quantified in the present study. However, utilizing another publicly available dataset, the Medication Expenditure Panel Survey, which reports US prescribing trends annually, some insight can be gleaned into the differing SGA prescribing rates within the United States. Data from the most recent year currently available, 2016, reveal that our study medications are prescribed at quite different rates, with quetiapine representing the 86th most commonly prescribed drug in the United States (8 751 996 prescriptions), aripiprazole the 131st (5 186 998 prescriptions), risperidone the 159th (3 975 563 prescriptions), and olanzapine the 225th (3 975 563 prescriptions).[16] However, the use of PRR as the primary outcome helps to limit the impact of this difference. Had total number of abuse-related events per medication been utilized as the primary outcome, the results of this study would be much more profoundly influenced by how often the medication is prescribed. Instead, PRR incorporates abuse-related events as a proportion of total events reported for each medication, and thus largely overcomes the biggest concern with differing prescribing rates. Beyond how often each medication is prescribed though, other prescribing patterns (eg, if one medication was prescribed more commonly to a group that is more vulnerable to SGA abuse than another medication) could influence the rate of SGA abuse. Given the limited demographics available in the FAERS database and the lack of well-defined risk factors for SGA abuse, it is difficult to quantify the level to which specific prescribing patterns of each of the four medications impact the results of this study.

Despite limitations, FAERS represents an important pharmacovigilance tool to identify early medication safety signals, including early signs of abuse liability, and the FDA recently highlighted the importance of utilizing FAERS data to remain abreast of shifting trends in prescription drug abuse.[17] Furthermore, this study adds to the previous body of literature by providing the first assessment of AERS data from the United States and the first to utilize AERS data to compare quetiapine with other comparator SGAs (aripiprazole and risperidone) in addition to olanzapine.

Conclusion

This study provides valuable insight from a large, nationally represented US cohort and corroborates the limited number of previous large-scale, systematic studies that have identified that quetiapine may possess a greater abuse liability than other SGAs. Given these data, caution may be warranted in prescribing quetiapine to patients with a history of, or risk factors for, substance use disorders. Additional prospective studies are needed to better characterize the abuse liability of quetiapine and other SGAs and to identify risk factors for abuse to inform health care practitioners regarding safe use of these medications.

Acknowledgements

This study was reviewed by the University of Texas Health San Antonio Institutional Review Board (Protocol Number HSC20180629N) and was deemed not human research, exempt from institutional review board approval.

Author Contributions

Study concept and design: KEE, CT, CRF, and SS. Statistical analysis: CT. Interpretation of data: KEE, CT, CRF, VGE, BF, and JH. Drafting of the manuscript: KEE, CT, VGE, BF, and JH. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: KEE.

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