

Emergency Department Visits Involving Misuse and Abuse of the Antipsychotic Quetiapine: Results from the Drug Abuse Warning Network (DAWN)

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ABSTRACT: Case reports in medical literature suggest that the atypical antipsychotic quetiapine, a medication not previously considered to have abuse potential, is now being subject to misuse and abuse (MUA; ie, taken when not prescribed for them or used in a way other than instructed by their health professional). Here we present systematic, nationally representative data from the 2005 to 2011 Drug Abuse Warning Network (DAWN) for prevalence of emergency department (ED) visits among the U.S. general population involving quetiapine and related to MUA, suicide attempts, and adverse reactions. Nationally, quetiapine-related ED visits increased 90% between 2005 and 2011, from 35,581 ED visits to 67,497. DAWN data indicate that when used without medical supervision for recreational/self-medication purposes, quetiapine poses health risks for its users, especially among polydrug users and women. These findings suggest that the medical and public health communities should increase vigilance concerning this drug and its potential for MUA.

KEYWORDS: misuse and abuse, quetiapine, emergency department visits, Drug Abuse Warning Network

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Introduction

Misuse and abuse (MUA) of pharmaceuticals is a major public health problem in the United States and occurs across a wide range of both prescribed and over-the-counter medications. MUA is associated with medications that produce euphoria (a high) or other desirable effect such as relaxation or alertness. Case reports in medical literature suggest that the atypical antipsychotic quetiapine, a medication not previously considered to have abuse potential, is being misused/abused by people. That is, it is taken when it has not been prescribed for them personally or is used in a way other than instructed by their health professional (eg, taken in greater amounts, more often, or for longer). Emergency department (ED) visits involving quetiapine are an indirect indicator of the use, misuse, and abuse of this drug. The number of visits by type (MUA, suicide, adverse reaction) and changes in these numbers over time can suggest the need for heightened awareness of the potential for MUA and the populations most at risk. Here we present systematic, nationally representative data depicting the prevalence of ED visits for the general population of MUA of quetiapine, suicide attempts involving quetiapine, and adverse reactions to quetiapine.

The array of antipsychotic drugs available has greatly expanded since the introduction of the first atypical antipsychotic

drug, clozapine, in the 1970s. The advent of numerous atypical or second-generation antipsychotics has provided new treatment options for those with serious mental illnesses such as schizophrenia and bipolar disorder and has largely replaced older classes of antipsychotics such as phenothiazines.^{1–3} Prescribing of atypical antipsychotic drugs has increased both for approved indications as well as for off-label uses.^{1,4}

Quetiapine (ie, Seroquel®) is a highly prescribed drug in the class of second-generation atypicals.⁵ Depending on its form (tablet or extended release), it is approved by the U.S. Food and Drug Administration for treating schizophrenia and certain types of bipolar and depressive disorders.^{6,7} Off-label prescribing of quetiapine is common.^{1,4,8} Clinical studies have established the effectiveness of quetiapine in treating psychiatric conditions, including obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, anxiety, and depression.^{3,4,8} Quetiapine has been suggested both as monotherapy or an add-on treatment for patients not responding to selective serotonin reuptake inhibitors and cognitive-behavioral therapy.³ Quetiapine has been used, with varying degrees of success, to aid in treating withdrawal symptoms from abused substances (ie, alcohol, cocaine, benzodiazepines, opioids) and increasing abstinence.^{9–21} These studies did not establish whether quetiapine works by improving comorbid



psychiatric conditions or by directly reducing craving.³ Quetiapine has been used to treat insomnia in patients in early recovery from alcohol dependence but with inconsistent results.^{22,23}

The main acute adverse effect of quetiapine is somnolence, and prescription labels warn to avoid using with alcohol.^{6,7} Other common effects (incidence $\geq 5\%$ and twice placebo) include dry mouth, dizziness, constipation, asthenia (weakness), abdominal pain, pharyngitis (sore throat), increased appetite, lethargy, elevated transaminase levels (indicating possible liver damage), and dyspepsia (upset stomach). When taken over longer periods, potential metabolic adverse events include rapid and significant weight gain, dyslipidemia, hyperglycemia, and diabetes.

Antipsychotics have not been typically viewed as recreational drugs or as having abuse potential because they do not produce a high and have undesirable sedating effects. There are signs, however, that quetiapine has emerged as a drug of abuse. These signs include the existence of street names and values for the drug, diversion in prisons and other institutionalized settings, users seeking the drug by feigning symptoms, and reports of intravenous or intranasal use of the drug. Starting in the early 2000s, case studies began reporting concerns about MUA of quetiapine. These early reports focused on illicit use in incarcerated populations,^{24–27} a problem that eventually resulted in regulatory measures to reduce the prescribing of quetiapine in custodial settings and, in some cases, to remove the drug from institutional formularies.^{28,29} Numerous case reports and several more systematic studies have shown that the problem of quetiapine abuse is not confined to penal populations and occurs in other settings and among other populations, such as psychiatric patients – both hospitalized and outpatient – and patients attending drug treatment clinics.^{11,12,28,30–41} Anecdotal evidence exists that patients attending emergency facilities and clinics demand quetiapine³¹ for malingering or fabricated psychotic symptoms, such as hearing voices.²⁴

Cubala and Springer³² reviewed 25 case reports of quetiapine use and abuse among psychiatric patients, published from 1966 to 2012, and identified the main users as males in their middle 30s; about half of users had a history of substance abuse or dependence. Fischer and Boggs³³ reviewed 12 case reports and found prior addictive behavior common among subjects in 10 of the 12 reports. These studies characterized subjects as polydrug users who had numerous psychoactive drugs prescribed, illegally obtained, and used pharmacologically and/or used quetiapine in combination with other drugs.^{33,42} In their study of 74 clients in a methadone maintenance program, McLarnon and colleagues³⁹ found that individuals with a history of misuse of anxiolytics, sedatives, or hypnotics were eight times more likely to report quetiapine misuse. Across these studies, use of quetiapine in conjunction with alcohol was often reported.

Users report seeking quetiapine (quell, Susie Q, baby heroin, squirrel) to self-medicate insomnia and anxiety, to get drunk without the hangover, to reduce the crash from stimulants such as cocaine, to zone out, to take the edge off, to isolate themselves from prison surroundings setting, to substitute for other drugs (jailhouse heroin), and to calm nervousness and anxiety after crack cocaine use.^{25,27,31} When used with other drugs of abuse, the combinations are referred to as Maq ball (quetiapine and marijuana)³⁵ and Q ball (quetiapine and cocaine or heroin).³⁰ Quetiapine is commonly diverted from prescribed users for its cash street value.⁴³

Quetiapine labeling carries the same warning as antidepressants for possible increased risk of suicidal thoughts and actions. Data on frequency of quetiapine overdose as a means of suicide come mainly from case studies detailing clinical treatment measures for overdose without systematic surveillance. Despite quetiapine's sedating nature, death or coma from overdose is relatively rare^{44–47} and the drug is generally well tolerated,^{48,49} although severe overdoses can require intensive hospital treatment.^{50,51}

Systematic knowledge is still sparse regarding the frequency of MUA of second-generation antipsychotics, especially quetiapine, in the general population. We present here the first report using nationally representative data from the United States to demonstrate prevalence of MUA of quetiapine in the general population seeking care at EDs for acute medical emergencies. We also include data on quetiapine involvement in suicide attempts and adverse reactions seen in the ED. We begin by examining descriptive statistics on quetiapine-related ED visits from 2005 to 2011 and then describe its use with other drugs, demographics of the user population, and measures of the seriousness of the ED visit as gauged by hospital admission subsequent to the ED visit.

Materials and Methods

Data. Data are from the Drug Abuse Warning Network (DAWN), a public health surveillance system that monitors drug-related ED visits.¹ Based on data appearing in ED visit records, DAWN reports on ED visits related to recent drug use. All types of drugs (licit and illicit drugs), alcohol, therapeutic substances such as nutraceuticals and herbal preparations, and over-the-counter medications are covered.²

DAWN relies on a probability sample of approximately 250–350 hospitals (depending on the year). DAWN cases are identified through the review of ED medical records in

¹Dawn is conducted by the Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, United States Department of Health and Human Services (CBHSQ/SAMHSA/DHHS).

²The classification of drugs used in DAWN is derived from the Multum Lexicon, copyright 2012 Lexi-Comp, Inc. and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the Lexicon can be found at <http://www.samhsa.gov/data/sites/default/files/MultumLicenseAgreement/MultumLicenseAgreement.pdf>.



participating hospitals. In 2011, more than 5 million ED visit charts out of a universe of 12.2 million charts at 233 reporting hospitals were reviewed, resulting in data of 229,211 drug-related ED visits that were used in estimation. A similar or higher number of ED visits were reviewed and abstracted annually from 2005 to 2010.

Counts of visits are weighted with population data to produce annual nationally representative estimates of drug-related ED visits for the United States and selected metropolitan areas.⁵² DAWN data tables are available at the SAMHSA web site,⁵³ and data files are available from the Substance Abuse and Mental Health Data Archive.⁵⁴ Counts deemed unreliable are suppressed in these sources.

This article discusses data related to the three main and mutually exclusive types of drug-related ED visits: (1) MUA, (2) suicide attempts, and (3) adverse reactions. MUA includes any nonmedical use or overmedication of a drug taken alone or in combination with other substances. This includes taking too much of a medication or taking a medication prescribed for another person. Suicide attempts include the misuse/abuse of drugs with the intent of harming oneself. Adverse reactions include visits in which patients used medications as instructed but experienced untoward effects.

Among visits involving multiple substances, DAWN does not indicate which drug(s) or substance(s) is/are responsible for the patient's presenting symptoms. A medication is not mentioned in the DAWN report if a patient regularly takes a medication for a medical condition (eg, insulin for diabetes) and the ED medical provider considers it incidental (not causal) to the reason for the visit. Toxicology testing is not systematically performed in all hospitals and therefore is not used in this analysis.

Disposition refers to the handling of the case after the initial stabilization in the ED. A patient who is admitted to the same hospital or transferred to another facility is considered to have been admitted or hospitalized. We use that outcome to imply that their medical emergency is more severe than that of patients who are treated and released or have other dispositions (eg, left against medical advice).

Quetiapine is a psychotropic drug that includes the classes of stimulants, anticonvulsants, antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics.

Questions examined. We examine the magnitude (estimates and percentage distributions) of ED visits involving MUA of atypical antipsychotics, including quetiapine. We present the (1) time trends, (2) demographics of patients, (3) combinations with other substances, and (4) disposition of ED visits (ie, treated and released vs. admitted). Similar measures are provided for ED visits involving a suicide attempt and for visits resulting from adverse reactions.

Analytic methods. Nationally representative estimates of drug-related ED visits were calculated using DAWN data that were weighted by first summing the case totals within

facility/month, applying the within-hospital weight, summing to the hospital level, applying the final hospital weight, and summing all hospitals. The calculations were performed using SAS® and SUDAAN®. Variance estimates and tests of significance were determined using the Taylor series linearization variance estimation method available in SUDAAN; for significance testing, we used the two-sample *t*-test procedure. Unless otherwise noted, all reported differences are significant at the $P < 0.05$ level.

Data presented herein were drawn for the period 2005–2011 for patients aged 12 years or older. After an initial examination of ED visits by year (Fig. 1), the seven-year annual average (2005–2011) is presented in subsequent tables.

Results

Prevalence and trends. Figure 1 shows the trends from 2005 to 2011 in ED visits involving quetiapine according to the reason for the visit (ie, MUA, suicide attempt, or adverse reaction). Overall, quetiapine-related visits for all three types of visits combined increased 90% during this seven-year period, from 35,581 visits to 67,497. The leading cause of quetiapine visits for each year was MUA. For each year, the proportion of visits for MUA was approximately 50%, whereas the share for either suicide attempt visits or adverse reactions each constituted approximately one-quarter to one-third of the total visits. The number of visits for MUA of quetiapine from 2005 to 2011 increased 67% from 19,195 to 32,024, but the difference did not reach statistical significance ($P = 0.06$); visits for suicide attempts increased significantly by 90%, from 8,645 visits to 16,413, and adverse reactions increased significantly by 146%, from 7,741 visits to 19,060.

Table 1 shows the annual average of ED visits from 2005 to 2011 for MUA, suicide attempts, and adverse reactions, which involved traditional (typical) antipsychotics or second-generation (atypical) antipsychotics. During this period, there was an annual average of 52,635 ED visits related to MUA of

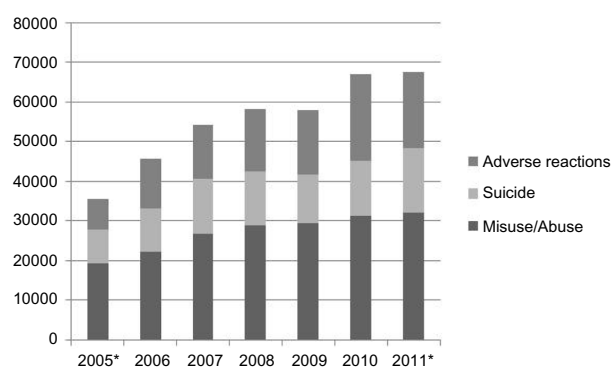


Figure 1. Trends in ED visits involving quetiapine for MUA, suicide attempts, and adverse reactions: 2005–2011.

Notes: *Comparing 2005 to 2011, visits are higher in 2011 for total visits at the $P < 0.001$ level, for suicide attempt visits at the $P = 0.03$ level, and for adverse reaction visits at the $P < 0.001$ level.

**Table 1.** ED visits for MUA, suicide attempts, and adverse events, by type of antipsychotics involved: annual averages, 2005–2011.

AGENT/CLASS	MISUSE/ABUSE		SUICIDE ATTEMPTS		ADVERSE REACTIONS		OVERALL	
	VISITS	%	VISITS	%	VISITS	%	VISITS	%
a All antipsychotics	52,635	100%	24,627	100%	66,336	100%	143,598	100%
b Atypical antipsychotics	43,409*	82%	20,615*	84%	43,205*	65%	107,228*	75%
c Clozapine	608	1%	153	1%	1,201	2%	1,962	1%
d Olanzapine	4,528	9%	1,869	8%	4,515	7%	10,911	8%
e Quetiapine	27,114+^	52%	12,769+^	52%	15,277+^	23%	55,160+^	38%
f Risperidone	5,804	11%	2,512	10%	9,024	14%	17,340	12%
g All other atypical antipsychotics	7,106	14%	3,818	16%	15,421	23%	26,345	18%
h Phenothiazines	2,740	5%	1,308	5%	8,868	13%	12,916	9%
i All other typical antipsychotics	8,901	17%	3,602	15%	17,902	27%	30,405	21%

Notes: *Visits involving atypical antipsychotics (b) are greater than visits for other antipsychotics (i) at the $P < 0.001$ level. +Visits involving quetiapine (e) are greater than visits for the sum of other atypical antipsychotics (c + d + f + g) at the $P < 0.001$ level. ^Visits involving quetiapine (e) are greater than visits for other antipsychotics (i) at the $P < 0.001$ level.

all antipsychotic drugs, with atypicals constituting 82% of the total or 43,409 visits. The greatest contributor to these MUA visits was quetiapine (27,114 visits; 52% of visits involving any type of antipsychotics and 62% of visits involving atypical antipsychotics). Olanzapine and risperidone accounted for a lower number of ED visits than quetiapine (4,000–6,000 ED visits each). Quetiapine was also the dominant atypical antipsychotic contributing to suicide attempts (12,769 visits; 52% of visits involving any type of antipsychotics and 62% of visits involving atypical antipsychotics). In contrast, the 15,277 quetiapine-related adverse reaction visits accounted for just 23% of adverse reaction visits involving any type of antipsychotics and 35% of visits involving atypical antipsychotics.

Demographics. Table 2 reflects a greater involvement of quetiapine for women than for men in MUA and ED visits related to suicide attempts. There is no difference between

men and women for adverse reactions. Considering age and sex, the number of ED visits involving MUA of quetiapine for women aged 40 or older is higher than that for men in the same age bracket; also higher are ED visits involving suicide attempts for women aged 12–17 and ED visits involving adverse reactions for women aged 60 or older. Considering all types of visits together, women have more quetiapine-related visits than men in all age groups except for those aged 18–24. There is no instance in Table 2 in which the number of visits for men is significantly greater than those for women.

Combinations. Table 3 shows the prevalence of ED cases for MUA, suicide attempts, and adverse reactions involving quetiapine in combination with other common licit and illicit drugs. About three-quarters of MUA visits and suicide attempt visits involved other drugs in addition to quetiapine. In contrast, only 52% of adverse reactions involved other drugs.

Table 2. Quetiapine-related ED visits for MUA, suicide attempts, and adverse events, by age and sex: annual averages, 2005–2011.

AGE	QUETIAPINE-RELATED ED VISITS															
	MISUSE/ABUSE N=27,094 (49%)				SUICIDE ATTEMPTS N=12,768 (23%)				ADVERSE REACTIONS N=15,277 (28%)				OVERALL N=55,139			
	MALES		FEMALES		MALES		FEMALES		MALES		FEMALES		MALES		FEMALES	
	VISITS	%	VISITS	%	VISITS	%	VISITS	%	VISITS	%	VISITS	%	VISITS	%	VISITS	%
12 to 17	818	7%	955	6%	183	3%	719*	10%	429	6%	243	3%	1,430	6%	1,917*	6%
18 to 24	1,996	17%	1,960	13%	932	17%	1,049	15%	710	10%	649	8%	3,638	15%	3,657	12%
25 to 39	4,019	35%	4,883	32%	2,263	41%	2,737	38%	1,476	21%	1,964	24%	7,758	32%	9,584*	31%
40 to 59	4,210	36%	6,617*	43%	2,068	37%	2,504	35%	2,625	37%	2,719	33%	8,903	37%	11,840*	38%
60 or older	592	5%	1,044*	7%	91	2%	222	3%	1,867	26%	2,595*	32%	2,550	11%	3,860*	13%
Total	11,635	100%	15,459*	100%	5,538	100%	7,231*	100%	7,107	100%	8,169	100%	24,280	100%	30,859	100%

Notes: *Visits for women are greater than visits for men at the $P < 0.05$ level. There is no instance where quetiapine-related visits for men are significantly greater than those for women.

**Table 3.** Quetiapine-related ED visits for MUA, suicide attempts, and adverse events, by other drugs found in combination and visit disposition: annual averages, 2005–2011.

2005–2011											
	MISUSE/ABUSE		SUICIDE ATTEMPTS			ADVERSE REACTIONS			OVERALL		
	VISITS	%	% ADMITTED	VISITS	%	% ADMITTED	VISITS	%	% ADMITTED	VISITS	% ADMITTED
All visits involving quetiapine	27,114	100%	50%	12,769	100%	83%	15,277	100%	27%	55,160	100%
Quetiapine alone	6,780	25%	44%	2,869	22%	82%	7,334	48%	22%	16,982	31%
All visits involving quetiapine in combination	20,334*	100%	52%	9,900*	100%	83%	7,944	100%	31%	38,178	100%
Alcohol	5,480	27%	59%	3,280	33%	80%	581	7%	44%	9,341	24%
Nonalcohol illicit drugs	4,400	22%	44%	2,464	25%	78%	^	^	^	6,864	18%
Cocaine	2,530	12%	49%	1,660	17%	82%	^	^	^	4,190	11%
Heroin	552	3%	50%	222	2%	80%	^	^	^	774	2%
Marijuana	1,583	8%	44%	857	9%	67%	^	^	^	2,440	6%
Pharmaceuticals (other than quetiapine)	16,804*	83%	51%	8,055*	81%	84%	7,673	97%	30%	32,532	85%
Anticonvulsants	3,853	19%	63%	1,748	18%	84%	2,562	32%	29%	8,163	21%
Antidepressants	6,673	33%	49%	3,212	32%	86%	3,570	45%	31%	13,455	35%
Relaxation drugs (anxiolytics, sedatives, and hypnotics)	9,287	46%	49%	3,872	39%	85%	3,038	38%	29%	16,197	42%
Barbiturates	142	1%	89%	^	^	^	^	^	^	224	1%
Benzodiazepines	7,729	38%	50%	2,996	30%	85%	2,502	31%	32%	13,227	35%
Narcotic analgesics	3,699	18%	47%	830	8%	80%	1,229	15%	35%	5,758	15%
Methadone	614	3%	65%	81	1%	78%	120	2%	^	815	2%

Notes: *Visits are greater than quetiapine alone at the $P < 0.001$ level. ^Data are suppressed because of patient confidentiality.



Across all three types of cases, the dominant class of drugs found in combination with quetiapine is pharmaceuticals, occurring in 85% of the visits. Among visits involving pharmaceuticals, anxiolytics, sedatives, or hypnotics are involved in about half of the visits for MUA and suicide attempts (55% and 48%, respectively); benzodiazepine is the most commonly reported drug in this class (83% and 77%, respectively). Anti-depressants are more commonly involved in adverse reactions (45%) than in MUA (33%) or suicide attempts (32%). Alcohol plays a role in about one-third of the MUA and suicide attempt visits involving quetiapine in combination but is infrequently observed in adverse events (7%). Illicit drugs (primarily cocaine, heroin, and marijuana) are found in combination in approximately 22%–25% of MUA and suicide attempts, but have negligible involvement in adverse events.

Disposition of the ED visit. Admission to the hospital after the ED visit (Table 3) showed different patterns, depending on the reason for the visit and whether multiple drugs were involved. Overall, 50% of patients who misused/abused quetiapine were hospitalized. Patients who misused/abused quetiapine in combination with other drugs were more likely to be hospitalized than patients using quetiapine alone (52% vs. 44%). Rates of admission for adverse events were lower than those for MUA: only 22% of patients seen for adverse reactions to quetiapine alone and 31% seen for quetiapine in combination were admitted. The highest rate of admission was for suicide attempts, with more than 80% of the cases admitted, regardless of whether quetiapine was used alone or in combination.

Rates of admission varied depending upon the particular substances involved. For example, considering MUA visits involving multiple drugs, admission rates ranged from 40% to 60% for most drugs. Rates for quetiapine–barbiturates combinations were notably higher (89%). For suicide attempt visits, rates of admission were about 80% for most quetiapine–drug combinations; rates for marijuana involvement were lower (67%). For adverse reactions, rates of admission were near 30% for all quetiapine–pharmaceutical combinations.³

Discussion

DAWN has contributed evidence that concern about MUA of quetiapine is warranted. As earlier reports have noted, quetiapine MUA has clearly spread beyond individuals in institutional settings and drug treatment programs to the general population. Acute medical emergencies involving quetiapine have almost doubled between 2005 and 2011. While the change in the number of ED visits related specifically to MUA of quetiapine over this period was just shy of being significant ($P = 0.06$), quetiapine is the most common antipsychotic leading to an MUA ED visit and accounts for over half of MUA visits involving antipsychotics. The precipitating events for these MUA visits may have been taking

too much quetiapine or, more likely, may be combining quetiapine with other substances, given that 75% of the visits were for quetiapine in combination. The finding of more frequent involvement of multiple drugs in quetiapine-related visits is consistent with previous smaller-scale studies. The higher levels of polydrug use involving quetiapine may suggest that deterrent efforts focus on persons with a history of polydrug abuse.

In contrast to some earlier studies, DAWN found that women in general seem more prone than men to have an ED visit involving quetiapine. This sex difference may have multiple explanations. Women are 70% more likely than men to experience depression during their lifetime.⁵⁵ Considering all types of drugs, DAWN found that women are more likely than men to be seen in the ED for a drug-related suicide attempt.⁵³ The Centers for Disease Control and Prevention similarly found that women are more likely than men to attempt suicide using poisoning – most commonly a drug overdose.⁵⁶ These factors, collectively, may place many women at higher risk of acute medical emergencies involving quetiapine.

The underlying reasons for the rates of quetiapine MUA are not currently fully understood. Increased prescription of this popular drug may provide greater opportunity for diversion, at least partially explaining increased ED visits. Studies in Australia have suggested that the increased availability of quetiapine as a result of prescribing trends is responsible for heightened ambulance rescues in metropolitan Melbourne from 2001 to 2010.³⁷ Although this provides strong support for increasing levels of adverse reactions, the relationship between prescribing levels and ED visits involving MUA and suicides is likely more complex. Heilbronn and colleagues posited that another potential driver of the rise in quetiapine-related harms may be increased quetiapine use among the illicit drug user population, a finding seen in other studies. This is consistent with our findings concerning polydrug MUA.

Although DAWN data do not allow us to address directly the reasons a person might abuse quetiapine, anecdotal evidence in the relevant literature suggests that abusers take quetiapine for its sedative effects when coming down from cocaine or other stimulants.^{12,13} The fact we did not observe cocaine as a major co-occurring drug in ED visits may be because cocaine and quetiapine taken together do not produce desirable effects or the combination is less likely to result in an acute medical emergency. Given the high co-occurrence with benzodiazepines, quetiapine may be used in conjunction with or as a substitute for benzodiazepines to self-manage the symptoms of withdrawal from other drugs of abuse. Another hypothesis advanced in the literature is that users seek quetiapine's effects to relieve intractable insomnia or anxiety. This is consistent with our finding of high co-occurrence of quetiapine with anxiolytics, sedatives, and hypnotics. The observation that other antipsychotics are not found as often in combination with this class of drugs may suggest that there are other factors influencing MUA of quetiapine. Other factors that

³Rarely will a visit attributed to adverse reaction involve an illicit drug.



may perpetuate continued use include marked withdrawal symptoms upon discontinuing quetiapine^{32,57} and the relative lack of extrapyramidal and other side effects that make it easier for illicit users to tolerate.³⁰

In the absence of definitive pharmacologic understanding of the basis of quetiapine's reinforcing properties, neurochemical explanations are, as yet, vague; some have implicated interplay between the antihistaminic properties of quetiapine and brain dopaminergic activity, a theory reminiscent of the long history of abuse of anticholinergic drugs for recreational purposes.⁵⁸ Direct action on the dopamine system per se is under debate, given the rather low affinity of quetiapine for dopamine receptors.³³ Future research can determine whether quetiapine itself produces a pleasurable high as typical drugs of abuse do in human or animal models.⁴⁰ Anecdotal reports from nonmedical users in blogs and web sites (eg, <http://www.bluelight.org>) reflect mixed viewpoints on the recreational value of quetiapine. Some users endorse the benefits of quetiapine use, whereas others are strongly adverse to its effects. These differences in individual preferences are not understood from a pharmacological point of view. It is unknown from the drug's pharmacologic properties, or human or animal studies, if quetiapine is intrinsically addictive, although intractable insomnia has been reported during cessation of the drug.³²

Quetiapine's role in suicide has not been systematically explored in the literature. We found that although generally the same types of drugs are taken in combination for both MUA and suicide attempts, the rate of hospitalization is nearly double for suicide attempt cases. This is not an unusual finding: in 2011, DAWN found that 75% of all drug-related ED visits involving suicide attempts resulted in admission to the hospital or transfer to another facility, regardless of the drugs involved.⁵³ Several explanations for these higher levels of hospitalization in suicide attempts are possible. The dosages of the substances (including quetiapine) may be greater for those with suicidal intent, the particular mix of substances may be more damaging in these cases, or suicide cases may be more likely to be hospitalized to allow for a period of psychiatric stabilization and/or medication adjustment. The longer term, more chronic adverse events of quetiapine are well studied. The drug's acute adverse reactions are less well known though excessive somnolence has been noted.

Limitations

DAWN relies on extant medical records that vary in specificity and detail. For example, ED records often do not distinguish if the drugs involved were legitimately prescribed or illegally obtained. Further limitations include the fact that DAWN does not collect dosage data or patient characteristics other than basic demographics. In cases of multiple drug involvement, it is not known which drug was the principal cause of the medical emergency leading to the visit. DAWN lacks data on the nature of the medical emergency or

whether the presenting cause was physical or mental health issues. Some authors have noted that patients with certain mental disorders that are sometimes treated with quetiapine may have a heightened risk of suicide. Without access to ED patients' other medical records, though, DAWN data are not sufficient to allow us to comment on the impact of these associations. For these various reasons, DAWN data are limited in their ability to provide detailed guidance to clinicians other than to suggest caution and vigilance when prescribing quetiapine.

Conclusions

By previous reports, quetiapine has emerged in the past decade as a potential drug of abuse with the features of more familiar recreational drugs such as having a street value and street name. The nationally representative data presented here show that large numbers of quetiapine-related ED visits involving MUA are occurring among the noninstitutionalized general population. When used without medical supervision for recreational/self-medication purposes, quetiapine poses health risks, sometimes serious enough to warrant an ED visit. Populations at higher risk appear to include women and persons abusing multiple drugs, although the reasons for their heightened risks appear to be different. These findings suggest the need for heightened vigilance both on the part of clinicians when evaluating potential misuse/abuse of quetiapine by patients and on the part of the public health community when planning drug abuse treatment programs and interventions. When prescribing quetiapine or treating patients known to be taking quetiapine, health professionals may need to be alert to the traditional signs of drug MUA (eg, requesting the drug by name, asking for early refills, stockpiling pills, and doctor shopping). Clinicians need to be especially concerned about MUA when prescribing quetiapine to patients with comorbid mental health and substance abuse issues or when using quetiapine as a therapy for substance abuse and dependence. This emerging public health problem merits continued surveillance and awareness on the part of prescribers and the public health community of the potential for misuse of this powerful pharmaceutical.

Author Contributions

Conceived and designed the experiments: MM, VA. Analyzed the data: VA, JY, CC, MM. Wrote the first draft of the manuscript: MM. Contributed to the writing of the manuscript: MM, VA, CC. Agree with manuscript results and conclusions: MM, VA, CC, JY. Jointly developed the structure and arguments for the paper: MM, VA, CC. Made critical revisions and approved final version: MM, VA, CC. All authors reviewed and approved of the final manuscript.

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