# The Interface

# Is Seroquel Developing an Illicit Reputation for Misuse/Abuse?

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.


## ABSTRACT

Quetiapine, an atypical antipsychotic, has been the subject of a series of case reports that suggest a potential for misuse/abuse. The available cases indicate a male predominance; oral, intranasal, or intravenous routes of administration; misuse/abuse in jail or inpatient psychiatric settings; and subjects with extensive histories of polysubstance abuse. While possible pharmacological explanations have been proffered, compared to the other atypical antipsychotics, there is no clear explanation for an alleged higher risk of misuse/abuse with quetiapine. Likewise, there are no available animal or human empirical studies to evaluate risk. At this juncture, clinicians in psychiatric and primary care settings can only remain alert to a potential risk, particularly in patients who meet the current demographic profile.



## KEY WORDS

Quetiapine, abuse, misuse


## INTRODUCTION

In this edition of The Interface, we examine the potential risk for misuse/abuse that has been inferred with the atypical antipsychotic quetiapine (Seroquel,™ Wilmington, Delaware). Quetiapine entered the market in 1997, and in 2008 generated sales of 4.5 billion dollars.[1] The drug has had a complicated pharmaceutical history, including concerns about the manufacturer allegedly not disclosing metabolic side effects and the United States Food and Drug Administration's (FDA) confrontation about off-label marketing.[2] Over the past several years, quetiapine has also been associated with case reports of patient misuse and abuse. In this edition of The Interface, we review the available evidence for misuse/abuse, examine potential pharmacological explanations, and discuss caveats.

## QUETIAPINE: A BRIEF PHARMACOLOGICAL DESCRIPTION

Quetiapine is a dibenzodiazepine atypical antipsychotic drug that is structurally similar to clozapine.[3] In terms of its receptor effects, quetiapine is a potent serotonin 5-HT2a-receptor antagonist and a moderate dopamineD2-receptor antagonist.[3] The drug also antagonizes serotonin 5-HT1a, dopamine $D_1$, histamine $H_1$, and adrenergic alpha$_{1/2}$ receptors, but has no meaningful activity at cholinergic, muscarinic, or benzodiazepine receptors.[3] The mean half-life of quetiapine is approximately

six hours.[3] At this juncture, quetiapine has been approved by the FDA for the treatment of schizophrenia and manic and depressive episodes as well as maintenance therapy in bipolar disorder.

## A DRUG OF MISUSE/ABUSE?

In assessing the evidence for quetiapine as a drug of misuse/abuse, we will present available case reports, published clinician impressions, the findings of cursory literature searches, and the emerging street character of quetiapine.

**Available case reports.** While presently designated as a non-controlled substance, there have been a series of case reports indicting quetiapine as a potential substance of misuse/abuse. These case reports are summarized in Table 1.[4–10] Note that the majority has involved younger male subjects and that the entire cohort is riddled with past substance abuse, particularly the abuse of benzodiazepines. The routes of misuse/abuse have included oral, intranasal, and intravenous entries, with the latter two methods mediated by crushing tablets. While not noted in the table, the majority of reported subjects were either incarcerated or psychiatric inpatients.

**TABLE 1.** Summary of case reports of quetiapine abuse

| FIRST AUTHOR (COUNTRY, YEAR) | PATIENT DEMOGRAPHICS | DESCRIPTION OF QUETIAPINE ABUSE | OTHER RELEVANT DETAILS |
|---|---|---|---|
| Paparrigopoulos[2] (Greece, 2008) | 48-year-old man | 1000mg /day orally | Alcohol/benzodiazepine dependence |
| Murphy[3] (US, 2008) | 29-year-old man | Unknown amount, orally | Feigned psychotic symptoms |
| Reeves[4] (US, 2007) | 49-year-old man<br>23-year-old man<br>39-year-old man | 800mg/day orally<br>2400mg/day, orally<br>800mg/day, orally | Alcohol/benzodiazepine abuse<br>Benzodiazepine dependence<br>Exaggerated bipolar symptoms |
| Pinta[5] (US, 2007) | 39-year-old man | 600mg/day, orally | Opiate abuse; demanded treatment with quetiapine |
| Morin[6] (US, 2007) | 28-year-old woman | Unknown amount, intranasally | Polysubstance abuse |
| Waters[7] (US, 2007) | 33-year-old man | 400–800mg, intravenously | Polysubstance dependence including benzodiazepines |
| Hussain[8] (Canada, 2005) | 34-year-old woman | 600 mg, intravenously | Polysubstance abuse, borderline personality disorder |

**Published clinician impressions.** In addition to the preceding case reports, there are a number of relevant professional commentaries in the published literature. For example, Hussain et al[10] state that, "…the [therapeutic] use of quetiapine [evolving] to its abuse either intranasally or intravenously is more prevalent than is currently assumed." Murphy et al[5] opine that, "…if the current misuse of the compound continues…then the abuse 'signal' will predictably become more evident…"[5] Pinta and Taylor[7] comment that, "We have not seen similar drug-seeking behavior with other second-generation antipsychotics…," with an emphasis that one of the authors has worked in the penal system for 35 years. Pierre et al[11] express their concern about the "widespread abuse" of quetiapine in the Los Angeles County Jail and disclose that, "…quetiapine is associated with a better subjective response than its conventional antipsychotic counterparts."[11] Keltner and Vance[12] state that, "…resourceful personalities have exploited the effects of quetiapine for its mind-altering effects," referring to the drug's abuse in prison populations. Finally, Hanley and Kenna[13] emphasize that, "Clinicians must be cognizant of the potential for quetiapine…as a drug of abuse."

**Cursory literature search.** Through a cursory search on the PsycINFO database, we entered the term *illicit use* with each atypical antipsychotic; only quetiapine yielded results in this literature. Likewise, we entered the term *abuse* with each atypical antipsychotic and, again, only quetiapine yielded findings.

**Street names and street value.** One final bit of substantiation of the veracity of quetiapine misuse/abuse relates to the various street monikers that have emerged as well as the assigned monetary street value. According to the published literature, street names for quetiapine include "quell,"[7,9,11,12] "Susie-Q,"[7,12] "baby heroin,"[9,12] and "Q-ball."[9,14] The last designation refers to the combination of quetiapine with another substance, such as heroin or cocaine. While not an official indictment of quetiapine, the development of street terms for any drug suggests some potential illicit value in this setting.

As for its explicit street value, Tarasoff and Osti[15] explored the cost of illicit quetiapine by soliciting the price of the drug from 61 buyers and sellers in Las Vegas, Nevada. A single-dose price for quetiapine 25mg was between $3 and $8. On a side note, olanzapine was the only other atypical antipsychotic that emerged in this study as a drug with street value.

## POSTULATED MECHANISMS EXPLAINING MISUSE/ABUSE

**The dopamine reward system.** According to Tcheremissine,[16] the contemporary theory of addiction posits that all addictive drugs share a common neurotransmitter explanation, which purportedly entails the dopamine system in the mesolimbic tract (i.e., the "mesolimbic reward system"). However, Tcheremissine adroitly points out that while the communal-pathway theory is appealing, this view is too "compartmentalized." Given this theory, how does quetiapine position with regard to dopamine influences when compared with the other atypical antipsychotics?

According to a summary of receptor potencies printed in the *Canadian Medical Association Journal*[17] and Horacek et al,[18] the potency of quetiapine at the D2 receptor site is relatively lower than most, if not all, of the remaining atypical antipsychotics. However, the overall effect is a decrease in dopamine. These data do not entirely exclude a dopamine-related explanation, but one would wonder why the other atypical antipsychotics are not at least equally subject to misuse/abuse.

**The sedation/anxiolytic theory.** Some authors suggest that the abuse potential of quetiapine may be mediated through its sedative/anxiolytic properties and therefore related to H1 and α1-adrenergic receptor antagonism.[4,6] However, existing data cast doubt on this hypothesis, as well. For example, quetiapine is less sedating than olanzapine[19] and comparable to clozapine.[20] Neither of these latter two atypical antipsychotics seem to be under scrutiny for misuse/abuse. In support of these reservations, Twaites et al[21] examined 1,728 patients on quetiapine; drowsiness and sedation were reported by only three percent of the entire cohort. Likewise, in a retrospective analysis of the quetiapine safety database (77 studies, 7894 patients), only 26 percent of participants reported somnolence at least once during quetiapine therapy.[22]

Finally, while abuse has been frequently associated with those who abuse or are dependent on benzodiazepines, quetiapine has no meaningful activity at benzodiazepine receptors.

**A cautionary note.** The seeming paucity of evidence for either of the preceding postulated theories does not exclude some unique intrinsic property of the compound that offers an appealing internal experience for users. Nor does this impression exclude the potential for quetiapine to be subject to abuse because of some unknown pharmacological effect (e.g., an anticholinergic effect) and/or unexpected additive effect with common substances of abuse. These possibilities warrant further research.

**Caveats.** To date, reports of quetiapine misuse/abuse have largely emerged from prison and inpatient psychiatric settings—unique settings that potentially limit the generalization of findings to more normative populations. In addition, most have occurred in individuals with extensive histories of substance abuse, particularly benzodiazepines, suggesting a likely risk factor for prescription. Indeed, in some cases, quetiapine appears to have been used in combination with an illicit drug to heighten a subjective effect—again, denoting a specific at-risk population. Finally, as Tcheremissine[16] rationally points out, there are no corroborating animal or human studies to either scientifically confirm or refute the risk of quetiapine misuse/abuse.

To complicate matters, quetiapine is being actively explored as a treatment for substance abuse. For example, quetiapine has been studied in cocaine dependence,[23] alcohol abuse,[24,25] polysubstance abuse,[26,27] cannabis use,[28] and opioid addiction,[29] and several studies have denoted its usefulness in dual-diagnosed patients. Curiously, the drug accused of misuse/abuse may be a treatment for those who misuse and abuse various substances.

## CONCLUSIONS

Quetiapine has been described in a number of case reports as a drug of potential misuse/abuse. At the present time, all cases have emerged from institutional settings, either prisons or inpatient psychiatric facilities. However, quetiapine has a number of street names and an assigned street value, which suggests that misuse/abuse may extend beyond the settings described in available case reports. The pharmacological theories to explain risk remain unsubstantiated, and there are no available animal or human empirical studies to clarify the potential risk. At this juncture, clinicians in psychiatric and primary care settings can only be alert to the potential for quetiapine to be misused/abused, particularly in patients with histories of polysubstance and/or benzodiazepine abuse and in those patients who unfoundedly pressure the clinician for the drug.

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