Quetiapine Abuse Fourteen Years Later: Where Are We Now? A Systematic Review

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\textbf{ABSTRACT}

\textit{Background:} Quetiapine, an atypical antipsychotic endowed with weak dopamine antagonist, potent 5-HT\textsubscript{2A}-blocking, partial 5-HT\textsubscript{1A}-agonist, anti-H\textsubscript{1} histamine, adrenolytic, and sigma; receptor agonist activities, since an original 2004 report is increasingly misused. Although some of its pharmacodynamics might explain some motives for voluptuary use, most of its actions are directed at setting-off those motives. Hence, it is possible that its popularity in special populations is due to the fact that the unpleasant or unwanted effects of addiction substances are somehow soothed by quetiapine. Currently, quetiapine is tested in substance use disorders, showing some promise, but it is likely to be misused in certain contexts. \textbf{Objectives:} To review the evidence for the use of quetiapine as addiction substance and investigate the characteristics of populations involved in such addiction. \textbf{Methods:} A systematic review of literature on various databases retrieved on September 7, 2018 87 records to comment. \textbf{Results:} We reviewed the evidence for quetiapine’s addictive potential in the light of its pharmacodynamics properties and presented two cases of recreational quetiapine use, by a 35-year old male patient with past addictive behavior and by a 50-year-old woman with major depressive disorder and conversion disorder. We found quetiapine to be abused mainly by addict populations and people with law involvement. \textbf{Conclusions/Importance:} There is no reason to include quetiapine among regulated substances, but monitoring of its use in selected populations is warranted. Psychiatrists and physicians working in the penitentiary system should be aware of the addictive potential of quetiapine and adopt measures restricting its use.

\textbf{INTRODUCTION}

The second-generation antipsychotic (SGA) quetiapine is widely used in clinical practice to treat psychosis and mood symptoms. This atypical antipsychotic drug has weak dopamine D\textsubscript{1}/D\textsubscript{2} antagonist, potent 5-HT\textsubscript{2A} antagonist, partial 5-HT\textsubscript{1A} agonist, H\textsubscript{1} histamine antagonist, \(\alpha\textsubscript{1}/\alpha\textsubscript{2}\) adrenoceptor antagonist, and sigma, receptor agonist properties. In the USA, it received approval for the treatment of schizophrenia in 1997, for bipolar mania in 2004, and for bipolar depression and major depression as an add-on in 2009. It has also been tested for its efficacy in non-psychotic symptoms, such as anxiety and insomnia (Srivastava, Patil, & Da Silva Pereira, 2013). It is usually administered orally; in the past it was used in higher doses the currently allowed maximum dose, i.e., 800 mg/day. It showed fair antipsychotic effects and efficacy as a mood stabilizer in the 400-800 mg/day range (George et al., 2013). It is available in two oral formulations, immediate- and extended-release. They are both available in quetiapine fumarate tablets of 50, 100, 200, 300, and 400 mg strengths; only the immediate release formulation has an additional 25 mg tablet form. The drug is approved for schizophrenia and bipolar disorder, while its extended-release formulation is also used as an add-on to antidepressants to treat major depression. Recommended daily doses range for adults from 150 mg to 750 mg for the immediate-release formulation with a maximum of 800 mg, and 400-800 mg for the extended-release, with the same maximum dose.

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\textbf{Supplemental data for this article can be accessed here.}
Is quetiapine endowed with a potential for treating or for inducing recreational substance use?

Antipsychotic drugs are generally considered devoid of abuse potential, and in spite of major concerns arisen, about 8% of incarcerated or other correctional populations engage in their nonmedical use (Bastiaens, Galus, & Mazur, 2016). However, quetiapine is not currently regulated as a schedule I or II substance under the US Code of Federal Regulations. Contrariwise, antipsychotics are tested and used in substance use disorders (SUDs), and quetiapine was found to be the only effective atypical antipsychotic in reducing cocaine use in a systematic review (Indave, Minozzi, Pani, & Amato, 2016). It is also used to ease symptoms triggered by other abused substances, including alcohol (Rech, Donahey, Cappiello Dziedzic, Oh, & Greenhalgh, 2015). However, several cases of quetiapine misuse have been recently reported (Piróg-Balcerzak, Habrat, & Mierzejewski, 2015). This led the manufacturers to introduce concerns about abuse, misuse, dependence, and withdrawal symptoms in their revised product monograph’s warnings and precautions (AstraZeneca Canada, 2017, p. 5). In literature, there is increasing concern for the misuse of quetiapine (Brett, 2015; Mattsson, Albright, Yoon, & Council, 2015; Peyrière, Diot, Eiden, & Petit, Réseau des Centres d’Addictovigilance, 2015; Anonymous, Prescrire International, 2016; James, 2016; Fountain & Slaughter, 2016; Montebello & Brett, 2017; Gjerden, Bramness, Tvete, & Slordal, 2017; Heeren & Farver, 2017; Chiappini & Schifano, 2018; Lee, Pilgrim, Gerostamoulos, Robinson, & Wong, 2018; Schifano, Chiappini, Corkery, & Guirguis, 2018), with still many questions (17 paper titles focusing this issue bear question marks in their titles, if we exclude the present paper), but few definitive answers.

We aimed to systematically review the evidence for abuse potential of quetiapine in literature and to present two case reports of inappropriate quetiapine use. In this review we will not follow the traditional pattern of pooling articles and then subdividing them according to subtypes to create chapters. We will instead follow a historical approach, a real-world one, including searching the Internet (the latter search’s results will be featured in the Supplement), we will attempt at hypothesizing the mechanisms whereby quetiapine might induce misuse, and provide two different case reports to underlie the multiplicity of the ways quetiapine could relate to its misuse.

Scientific literature review

A PubMed/Medline search carried out on 7-September-2018 using the strategy “(Quetiapine OR Seroquel OR ICI 204,636) AND (abuse OR misuse OR addiction OR dependence OR addict OR addicted OR nonprescription OR non-prescription OR illicit OR recreational OR voluptuary OR off-label[ti])” yielded 468 records spanning from August 1998 to August 16, 2018 [Epub ahead of print], of which 66 were relevant. The same search on CINAHL on the same day produced 99 records, of which 28 were relevant and added 8 to PubMed. PsychINFO/PsychARTICLES found 289 records of which 6 were new to PubMed and CINAHL, while the Cochrane Library (same strategy but no [ti] used) found 155 records of which 1 was relevant and added none to other searches. Relevant records spanned from September 2004 to May 4, 2018; there were four extra-database articles from the reference lists of identified records to add to the 80-record output and this brought the number of records to consider to 84. Three additional studies resulted from internet searches (Google and further journal sites), thus, the final grand total was 87. Six independent reviewers (AEV, GDK, MC, CR, VS, and MC) reached consensus through Delphi rounds (three were enough to this end). Searches and their results are shown in Figure 1 in a non-PRISMA–like format, despite we followed the PRISMA statement guidelines in conducting our systematic review (Moher, Liberati, Tetzlaff, & Altman, PRISMA Group, 2009). This we did because strictly following the PRISMA figure would have resulted in curtailing the amount of specific information we needed to convey. However, we included the PRISMA flowchart in the Supplement.

The discovery of quetiapine’s addictive potential

Excluding cases of accidental or intentional self-harm intoxications, it took seven years of clinical use of the drug in the US for a report on its misuse to appear in literature (Pierre, Shnayder, Wirshing, & Wirshing, 2004). Since the original 2004 report, reports and comments waxed and waned, but in recent years, starting from 2015, increased interest is witnessed by the number of papers published on the issue; in 2018, seven articles have already appeared. Now, 14 years later, the literature is growing, but its inconsistency leaves no space for clear cut conclusions. The per year output of PubMed is shown in Figure 2.

Special populations?

The abuse of prescribed medications among inmates is already known to healthcare professionals (Oyemade, 2010; Tamburello, Lieberman, Baum, & Reeves, 2012). In fact, most case reports refer to quetiapine abuse in prison (M. Z. Hussain, Waheed, & Hussain, 2005; Pinta & Taylor, 2007; Kaya, Dilbaz, Okay, & Çeşmeci, 2009; Fischer & Boggs, 2010; Srivastava et al., 2013; Klein-Schwartz, Schwartz, & Anderson, 2014) or during court-ordered hospitalization (Morin, 2007). However, several reports suggest that quetiapine is commonly abused also among psychiatric outpatients (Waters & Joshi, 2007; Reeves & Brister, 2007; Murphy, Bailey, Stone, & Wirshing, 2008; Chen et al., 2009). Furthermore, the development and the diffusion of street forms of quetiapine (Srivastava et al., 2013) and the manipulation of its pills, for example, crushing and subsequent snorting (Morin, 2007), or intravenously injecting (Gugger & Cassagnol, 2008) or smoking (Haridas, Kushon, Gurmu, & Oluwabusi, 2010), suggest its abuse potential.

Not just inmates

Among psychiatric patients who abuse quetiapine, half abuse street drugs as well, most notably heroin and cocaine.
Quetiapine has established some reputation among addicts as a misused substance (R.A. Sansone & Sansone, 2010; Dobbin, 2014; Anonymous, *Primary Care Drug Alerts*, 2015; Motta-Ochoa, Bertrand, Arruda, Jutras-Aswad, & Roy, 2017), even in pediatric cases (Kolli, Mary, Garcia-Delgar, & Coffey, 2016). It is colloquially known as “Quell”, “Sus(z)ie-Q”, “baby heroin”, “Snooze berries” (Pierre et al., 2004; Pinta & Taylor, 2007; Waters & Joshi, 2007), “Q”, and “Squirrel”, while “Q-ball” or “Rosemary’s Dolly” is a combination of quetiapine and cocaine (Waters & Joshi, 2007) and “Maq ball” is quetiapine mixed with marijuana (Haridas et al., 2010).

**How is quetiapine taken and how is it obtained?**

Quetiapine abuse occurs through various routes of administration. Intravenous (Hussain et al., 2005; Waters & Joshi,
剞sive quetiapine off-label (Peyri et al., 2012) addressed by the physicians themselves, who do not pre-

A deadly habit?
The prevalence of recent abuse of quetiapine fumarate in a population of people who self-injected illicit drugs was found to be 15% (Reddell et al., 2014). Quetiapine, compared to risperidone and olanzapine, is more likely to be abused (S. Kim, Lee, Kim, Jung, & Chang, 2017; Klein, Bangh, & Cole, 2017). Quetiapine abuse was found to be related to significantly more harms and ambulence interventions, and this was most frequently encountered in populations who were regularly using other drugs (Heilbronn, Lloyd, McElwee, Eade, & Lubman, 2013; Kim et al., 2017). The reported quetiapine-related fatalities (Pilgrim & Drummer, 2013) usually occur in multisubstance use contexts (Haukka, Kriikku, Mariottini, Partonen, & Ojanperä, 2018). Among 20 cases in Virginia where quetiapine ingestion was documented, three were positive for history of drug abuse; in all cases, other substances were also taken and in two of them, one of which was presumably a suicide case, cocaine ingestion was involved. In all three cases, pathologists found visceral congestion, and lung and liver alterations (Flammia, Valouch, & Venuti, 2006). Quetiapine is increasingly detected in deceased people’s blood in the Western world (Papoutsis et al., 2017).

Quetiapine addiction? possible mechanism of reinforcement

People engaging in quetiapine misuse attribute it to its purported sedative, hypnotic, anxiolytic, calming, and hedonic effects, with some aiming at “highs”, while others, who feel dangerously high or use it conjointly with stimulants, use it seeking “downer” effects pointing to a modulation of the effect of stimulants (Pierre et al., 2004; Hussain et al., 2005; Reeves & Brister, 2007; Morin, 2007; Murphy et al., 2008; Paparrigopoulos et al., 2008; Anonymous, Alcoholism & Drug Abuse Weekly, 2009; Fischer & Boggs, 2010; Heilbronn, Lloyd, McElwee, Eade, & Lubman, 2012; Srivastava et al., 2013). However, at odds with this tendency to render perceptions smoother, a case has been described of a patient aiming at experiencing hallucinogenic effects by snorting crushed quetiapine combined with cocaine (Waters & Joshi, 2007) (see also Supplement).

In most cases, abusers are psychiatric patients taking other drugs or individuals with a history of specific SUD (Capece & Pavlovsky, 2016) or polyabuse (Hussain et al., 2005; Morin, 2007; Waters & Joshi, 2007). People abusing quetiapine usually start with low doses and subsequently increase them, gradually stopping all other medications or illicit drugs and leaving only quetiapine at increasingly higher doses (Pinta & Taylor, 2007; Fischer & Boggs, 2010; Srivastava et al., 2013). However, occasional misuse-related overdose in an addict may result in life-threatening side effects (Jhaveri & Webber, 2008).
When clinicians attempt at gradually tapering quetiapine, patients report restlessness, irritability, sleep disturbances, and quetiapine craving (Srivastava et al., 2013). However, even dose increases may lead to similar results; in fact, a patient who increased his dose obtained no clinical improvement, but rather a worsening of irritability and insomnia (Fischer & Boggs, 2010). It appears that the well-known anti-insomnia effect of quetiapine undergoes tolerance and dose escalation with time (Cornelis et al., 2016). On the other hand, quetiapine has been found to be able to reduce alcohol craving in patients with alcohol use disorder and psychosis (Martinotti et al., 2008) and opioid withdrawal in patients with opioid addiction (Pinkofsky et al., 2005).

**Culture**

In correctional settings, prisoners feigned psychosis to obtain quetiapine (Caniato, Gundabawady, Baune, Alvarenga, 2009), or threatened legal action and even suicide should quetiapine administration be discontinued, something that does not occur with other second-generation antipsychotics (Pinta & Taylor, 2007). To our knowledge, there is only one report in the literature of successful discontinuation of quetiapine and subsequent removal from a correctional formulary (Tamburello et al., 2012). Another study focused on prison psychiatrists’ education about the use of low-dose quetiapine for insomnia and showed a 59% reduction of its prescription 22 months after education (Reeves, 2012). This study focused on the removal of quetiapine from prison formularies of several institutions without naming them, and did not report on inmate requests for the drug, but rather focused on physicians’ behavior.

All the above points to a certain addictive potential of quetiapine, while similar data have not been reported for other SGAs, making quetiapine the only known SGA with pressing requests on behalf of patients for its prescription (Monasterio & McKeen, 2013).

The lower propensity of quetiapine to induce untoward effects may contribute to the fact that quetiapine has a higher misuse potential than other SGAs (Fischer & Boggs, 2010; Grabowski, 2018); however, movement disorders related to quetiapine misuse have also been described (Desarkar, Desarker, & Sinha, 2006; Aggarwal & Jiloha, 2008; Rizos, Douzenis, Gournellis, Christodoulou, & Lykouras, 2009; Shah, Grover, Maheshwari, Kate, & Malhotra, 2010), and there has been a recent report of acute dyskinesia, myoclonus and akathisia in an adolescent using quetiapine via nasal insufflation (George et al., 2013). Other reasons may rely on specific settings; for example, in correctional settings, quetiapine is more available than other drugs, thus explaining its non-medical use among inmates (Hussain et al., 2005). Further reasons may be found in the Supplement.

**Chemistry**

Leaving aside the complex pharmacodynamic properties of quetiapine and its multireceptor involvement in its actions (Cross et al., 2016), the timeline of dosage increase in quetiapine abuse suggests that its pleasurable effects undergo tolerance, thus needing progressively higher doses, like in opiate abuse. Although quetiapine does not bind the μ-opioid receptor, differently from haloperidol, which is a sigma receptor-antagonist and generates an unpleasant cue, it is an agonist of the sigma-receptor (Kotagale, Mendhi, Aglawe, Umekar, & Taksande, 2013). This site, originally classified as an opioid receptor, interacts with many endogenous substances like sphingolipids (Ramachandran et al., 2009), opioid peptides, neurosteroids (Guitart, Codony, & Monroy, 2004) and as yet unknown “sighmaphins” (Su, Weissman, & Yeh, 1986); it is also specifically activated by the endogenous hallucinogenic N,N-dimethyltryptamine (Fontanilla et al., 2009). The sigma site is stimulated by abused drugs like ketamine (Nakao, Miyamoto, Masuzawa, Kambara, & Shingu, 2002), phencyclidine (Sharp, 1997), methamphetamine, and cocaine (Yasui & Su, 2016). Alternatively, quetiapine has post-membrane mechanisms that are not shared by other antipsychotics. Quetiapine induced rodent p90RSK phosphorylation followed by decreased p90RSK levels and increased c-fos levels in the ventral (limbic) striatum/accumbens. This effect in rodents depended on the epidermal growth factor receptor (EGFR) and involved the extracellular signal-regulated kinase (ERK) cascade (Pereira, Zhang, Malcolm, Sugiharto-Winarro, & Sundram, 2014). Quetiapine thus controlled synaptic plasticity with this mechanism. It should be mentioned here that plasticity has been variously involved in addictions (Lu, Koya, Zhai, Hope, & Shaham, 2006; Sun, Quizon, & Zhu 2016). Hence, it is possible, in case plasticity changes like those shown in animals be demonstrated in humans, that quetiapine-induced interference with intracellular cascades could offer a viable way to investigate the biological underpinnings of addiction.

**Animal studies**

The co-administration of quetiapine and amphetamine in the rat results in anxiolytic effects, while leaving the reward properties of amphetamine unaltered (McLelland, Martin-Iverson, & Beninger 2014). Furthermore, quetiapine in Rhesus monkeys reinforces low-dose, but not high-dose, cocaine self-administration (Brutcher, Nader, & Nader, 2016), without affecting sleep parameters (Brutcher & Nader, 2015). However, caution is needed when interpreting these results, as animals (even primates) are not humans (Sánchez & Ellenbroek, 2017). Symptom worsening in humans after increasing quetiapine doses may be due to sigma-site agonism, which no other antipsychotic than quetiapine is known to activate. A similar symptom-worsening due to quetiapine abstinence and withdrawal is more likely to involve other, biogenic amine-related mechanisms. However, mechanisms like fast dissociation from dopamine receptors (Kapur & Seeman, 2000; Tauscher et al., 2004; Srivastava et al., 2013) or prefrontal dopamine release mediated by 5-HT1A receptor activation and 5-HT2A inhibition (Kuroki, Nagao, & Nakahara, 2008) that could explain some effects, are shared by other SGAs which did not demonstrate a similar abuse potential. Cholinergic mechanisms may come into play in mental state alterations due to overingestion of quetiapine; in fact, these may be reversed by the muscarinic
cholinergic agonist physostigmine (Cole, Stellpflug, Ellsworth, & Harris, 2012). Another mechanism that could be involved is noradrenaline transporter (NET) inhibition, since norquetiapine, the active metabolite of quetiapine, behaves like many antidepressants that inhibit NET (Srivastava et al., 2013; Cross et al., 2016), besides having partial 5-HT1A receptor agonist, and presynaptic α2-adrenoceptor, serotonin 5-HT2C and 5-HT7 receptor antagonist activities that might contribute to this effect (López-Muñoz & Álamo, 2013). However, the potent anti-H1 effect of quetiapine may also play a role in quetiapine’s recreational use, in that it may enhance dopaminergic activity in the N. accumbens, considering the low propensity of the drug to block dopaminergic D1 and D2 receptors (Fischer & Boggs, 2010; Aa, Helland, & Spigset, 2012).

Does the formulation matter?

Interestingly, when at the Florida Department of Corrections it was decided to shift from the immediate-release to the extended-release (XR) formulation of quetiapine, which has a delayed and blunted serum peak with respect to the former, those inmates who had previously abused immediate-release quetiapine admitted to their interviewing doctor that they liked considerably less the effects of the XR formulation, even after manipulating the drug (Reccoppa, 2011). This suggests that the XR formulation is less likely to be abused; consequently, its use in correctional (Reccoppa, 2011) and clinical settings is more recommendable, or rather, the immediate-release formulation should be avoided. However, it is unclear whether the formulation, immediate- or extended-release, affects plasma levels of quetiapine (Chouinard et al., 2017), and as we will see later, the latter may also be used unsupervised and off-label by patients. The two formulations differ in their pharmacokinetic profiles by little and this does not affect the overall absorption or elimination of quetiapine (Figueroa, Brecher, Hamer-Maansson, & Winter, 2009) or norquetiapine (Datto, Berggren, Patel, & Eriksson, 2009). However, brain D2 dopamine receptor occupancy with extended-release quetiapine is less pronounced and more enduring than the one observed for the immediate-release formulation; occupancy peaks later, is lower, and troughs later with the former (Nord et al., 2011). This may affect dopamine receptor occupancy in pleasure perception areas, providing different ranges of options that could suit any taste, i.e., “high kicks” or feeling “slack” and “loose”.

Other antipsychotics with similar receptor profiles and antihistaminic effects did not show an abuse potential similar to that of quetiapine (Fischer & Boggs, 2010), although across the years, many psychoactive medicines have been blamed as potentially abuse-related, including older and newer antidepressant, anticholinergic, antiparkinsonian, and first generation antipsychotic drugs (Tcharernissine, 2008; Bogart & Ott, 2011), but also antiepileptic (Hawkins & Gidal, 2017) and antihistaminic drugs (Goldin, 1989). The study of the difference at this regard between quetiapine and other antipsychotics deserves further research.

Two case reports, one typical and one atypical

Case 1

As an example, we report a case of quetiapine abuse in a patient with alcohol addiction and previous abuse of other psychoactive substances. This Italian 35-year-old Caucasian man with Bipolar Disorder type II was seen at a local mental health service while having a major depressive episode with a strong anxiety component. In addition to citalopram (10 mg/day) and quetiapine (50 mg/day), he received psychological support and psychoeducation. He initially denied any form of alcohol or psychoactive substance use, but after a few visits, he admitted in the presence of his parents that he occasionally took 600-800 mg of quetiapine in the evening, falling in a state of narrowed consciousness, with strong euphoria and disinhibition. He reported cannabis and alcohol abuse since age 15. At age 18 he also used cocaine, MDMA, LSD and Salvia Divinorum in recreational contexts. From the age of 25 years onward he regularly drank 1.5-2 liters of beer a day, starting late in the afternoon, the time at which craving usually emerged. His motive for accessing our service was to cope with the negative mood emerging after his attempts at quitting alcohol. As he was living with his parents, he was exposed to their blaming on alcohol drinking and to their encouraging to adopt a non-drinking style. After realizing that he abused quetiapine to substitute for the effects of alcohol, he was prescribed aripiprazole (10 mg/day) and referred to a specialized service for addictions. At follow-up, he reported quitting quetiapine, but he had shifted to alprazolam, at least 3 mg, taken late in the afternoon.

Case 2

Another case regards a 50-year-old Italian Caucasian woman with a major depressive disorder diagnosis, comorbid with conversion disorder who was on 150 mg oral bupropion in the morning, 6 mg oral clonazepam and 50 mg oral immediate release quetiapine late in the evening, and 25 mg daily oral pregabalin (which she did not tolerate and soon suspended), that were prescribed her at our day hospital. Since she responded poorly to medication, she discontinued bupropion and referred to our outpatient service for the first time, where we introduced 4 mg reboxetine, leaving clonazepam administration unaltered. The patient had a drive to accumulate prescription drugs and was seeing many physicians to obtain prescriptions of drugs that she subsequently bought, stored and then used at her discretion. As non-response continued, she abandoned reboxetine and took autonomously oral prolonged-release (XR) quetiapine (which she had accumulated through earlier prescriptions), increasing her doses from 25 mg to 150 mg, reintroducing increasing doses of bupropion from 150 mg to 300 mg. She returned to our outpatient facility five months later, during which she had developed an agitated depressive state. We tapered-off bupropion, switched quetiapine to 50 mg immediate-release, and started her on amisulpride at a daily oral dose of 50 mg. One month later, her mood symptoms subsided and her clinical state stabilized, with only
few residual somatic symptoms. Four months later, she maintained treatment response. The clinical picture was unchanged.

**Discussion of case reports**

It is possible that the first patient’s shift to alprazolam to compensate for the lack of voluptuary effects of alcohol and quetiapine could be related to the fact that all these substances interact with receptors modulated by neurosteroids, like GABA and sigma receptors (Yamamura et al., 2009; Blasio et al., 2015). Since NMDA receptor activity is also modulated by sigma receptors and neurosteroids, it is possible that the patient sought a kind of dissociative effect of the drugs he used in the evening. Dissociative effects may be liked and sought after by people keen to use recreational drugs (Caloro et al., 2018). The interplay between aminoacidergic and monoaminergic systems might have influenced one patient’s choice described in literature to abuse concomitantly quetiapine and gabapentin, which he reported to produce a simultaneous state of sedation and euphoria (Reeves & Burke, 2014).

The second case is interesting as it is a first case of dose escalation of extended-release of quetiapine, concurrent with non-therapeutic use of bupropion, a dopamine/noradrenaline reuptake inhibitor. Although few reports of abuse were reported with bupropion, its dopamine reuptake blocking properties are likely to generate a cocaine-like cue (Vento et al., 2013). It is unexplainable how a drug use-prone patient can prefer a combined hyper-dopaminergic state caused by one drug and a hypodopaminergic one caused by another drug. While at low doses, quetiapine may selectively increase mesocortical transmission through autoreceptor blockade, increasing doses may block dopaminergic transmission at all levels. The patient recovered on low-dose amisulpride, a substituted benzamide that is used at low doses as an antidepressant in Italy, which is effective at low doses against the negative symptoms of schizophrenia, with the rationale that it selectively activates prefrontal dopaminergic activity (Boyer, Lecrubier, Puech, Dewailly, & Aubin, 1995).

The diversity between our case reports shows the many facets of the motives that promote addictive behavior. What is shared between our patients is the wish to avoid harm or disagreeable situations, rather than to seek pleasure.

**Limitations**

The literature on the addictive potential of quetiapine is cumulating through the years, but the quality of the evidence is poor and anecdotic. There is a lack of controlled studies that would allow us to draw firm conclusions. Most evidence comes from case reports and occasional observations. The issue needs to be explored systematically.

**Conclusions**

Quetiapine is not generally a drug that tends to be abused in the general population, but may be sought after for its antianxiety and dissociative effects by specific patients and may be abused by special populations, like prison inmates for reasons having to do with placebo responses and an effect similar to disease mongering, i.e., the creation of mythical ideas about its pleasurable effects. For this reason, although we believe there is no reason to change the Schedule of quetiapine in the US Code of Federal Regulations, lest to limit its therapeutic potential, its use should be monitored in special populations, especially people prone to recreational drug use and prison inmates. The pictures emerging from the overview of scientific literature and from lay persons’ blogging only partially overlap.

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