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Quetiapine in Substance Use Disorders, Abuse and Dependence Possibility: A Review

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Abstract

Quetiapine is an atypical antipsychotic approved by the FDA (Food and Drug Administration) for use in the treatment of schizophrenia, acute mania, and bipolar depression. Pharmacologically, it has antagonistic effects on serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D_1 and D_2, histamine H_1, and adrenergic α_1 and α_2 receptors. In addition to reports of its use in schizophrenia and bipolar disorder, many studies have examined the use of quetiapine in the treatment of anxiety disorders and substance use disorders. In the treatment of patients with psychotic or bipolar disorder with a comorbid substance abuse disorder even though quetiapine was prescribed primarily for the treatment of the underlying psychotic symptoms, patients taking this medication reported a significant reduction in substance use. Yet, there are also case reports of quetiapine abuse and dependence; in particular among prisoners and patients diagnosed with substance abuse. Though quetiapine should be used peroral, it is also used intranasally and intravenously in these patient groups. Moreover, in some cases quetiapine is combined with other substances, such as cocaine or marijuana, to increase sedation. This abuse of quetiapine is thought to occur due to the anxiolytic and sedative effects of the drug. There are no controlled studies on quetiapine dependence in the literature and it remains unknown whether or not quetiapine causes dependence. This review aimed to present all published case reports on quetiapine abuse and to discuss the possible mechanisms that underlie its abuse and dependence.

Key Words: *Quetiapine, abuse, dependence, substance use disorders*

INTRODUCTION

Quetiapine is considered as an atypical antipsychotic and has been approved by the FDA (Food and Drug Administration) for use in the treatment of schizophrenia, acute mania, and bipolar depression. Quetiapine, a dibenzodiazepine derivative, is pharmacologically similar to clozapine and has an antagonistic effect on serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D_1 and D_2, histamine H_1, and adrenergic α_1 and α_2 receptors (Goldstein 1999; Reeves and Brister 2007; Riedel et al. 2007). In addition to its similarity to clozapine, quetiapine has the advantage of not causing agranulocytosis. Its affinity for 5-HT_{2A} receptors is much stronger than its affinity for D_2 receptors; consequently, it is thought to cause fewer *extrapyramidal side effects* (Green 1999). Furthermore, *hyperprolactinemia that is another side effect of antipsychotics* , *is less frequently encountered with* quetiapine use.. Unlike other atypical antipsychotics, the fact that quetiapine temporarily attaches to postsynaptic D_2 receptors and detaches from them in a short time contributes to its reliable side effect profile (Kapur et al. 2000). At the lower end of quetiapine's suggested dosage level (50-750 mg/day) is thought that it does not have any significant affinity for cholinergic muscarinic receptors or benzodiazepine receptors. Nevertheless, doses above 500 mg/day more frequently cause anticholinergic effects, such as dysuria, constipation, and dry mouth (Morin 2007).

Apart from quetiapine's use in schizophrenia and bipolar affective disorder, an extensive body of research on its off-label use exists. In Rowe's (2007) study, authors added low doses of quetiapine to the treatment of resistant cases when, in particular, selective serotonin

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re-uptake inhibitors and cognitive behavioral therapy remained inadequate. Thus, it was reported that quetiapine is suggested for patients with obsessive-compulsive disorder, prost-traumatic stress disorder, substance use disorder, personality disorder, and anxiety and depressive disorder. Similarly, a study conducted by Philip et al. (2008) analyzed prescriptions over a 2-year period and reported that quetiapine was mostly used off-label in the treatment of depression, followed by the treatment of bipolar and psychotic disorders comorbid with substance use disorder. In addition, a growing number of case reports on the misuse of quetiapine have been published (Pierre et al. 2004; Hussain 2005; Morin 2007). It is noteworthy that these cases generally consist of prisoners and patients with a history of multiple substance dependence. When designing and monitoring treatment, doctors particularly interested in these groups of patients should be careful about the use of quetiapine alone or in combination with other substances that might or might not be addictive.

Quetiapine use among prisoners that were brought from a closed prison in the town to the psychiatric clinic of Osmaniye State Hospital for medical examination, have some similarities to cases of quetiapine abuse reported in the literature. In all, 14 prisoners out of 330 were prescribed quetiapine, and these prisoners were diagnosed with multiple substance use and antisocial personality disorder. It was reported that the quetiapine treatment began before or after imprisonment at various clinics and that the prisoners insisted on using quetiapine. In fact, some of the prisoners refused to leave the interview room unless they were prescribed quetiapine. In particular, patients with a history of substance dependence consistently demanded quetiapine from the prison doctors, and they did not want to use drugs with sedative effects, such as mirtazapine and trazodone, which were prescribed by psychiatrists. The prison guards and doctors observed that the prisoners attempted to give quetiapine to each other. Additionally, during psychiatric interviews some prisoners reported that they collected quetiapine given to them as a daily dose, and then consumed 600-800 mg of quetiapine in a single dose in order to feel calm.

METHOD

This review, written based on the reports mentioned above, aimed to examine published case reports on the possible abuse of quetiapine and quetiapine dependence, as well as the relationship between substance use disorder and quetiapine. To meet this objective the Turkish and foreign psychiatric publications were searched. Turkish and foreign articles published between 1990 and 2009 were searched through the Turkish national (ULAKBİM Türk Tıp Dizini, Türk Psikiyatri Dizini) and international databases (PubMed, EMBASE, and ISI Web of Science) using different combinations of the key words mentioned in the abstract. Case reports, reviews, and meta-analyses were searched, and those that were appropriate for this review were examined.

Quetiapine in the Treatment of Substance Use Disorders

The use of quetiapine in the treatment of substance use disorders has been studied in populations of patients diagnosed with comorbid schizophrenia and bipolar disorders (Brown et al. 2002; Sattar et al. 2004; Martinotti et al. 2008). Substance use disorders were diagnosed 2-3 times more frequently in patients with schizophrenia than in the control group (Potvin et al. 2008). This high comorbidity rate is thought to originate from the common biological roots of these two disorders. It was posited that dopamine sensitivity in the schizophrenic patients made them more susceptible to the rewarding effect of the substance (Hanley and Kenna 2008). In addition, the endogenous cannabinoid system is thought to play a role in both disorders (Potvin et al. 2008). Similarly, about 50% of patients with bipolar disorder had a history of substance abuse disorder (Brown et al. 2002).

After antipsychotic treatment was administered to control psychotic symptoms it was observed that the quantity of substance used by patients decreased (Volkow et al. 2002). On the other hand, some studies reported that antipsychotic use increases the amount of substance used by patients diagnosed only with a substance use disorder (McEvoy et al. 1995). These differing results are thought to be the result of variation in the mechanisms of effect of different antipsychotic drugs. While low-potency antipsychotics decrease the quantity of substance taken, high-potency antipsychotics increase the quantity taken (Sattar et al. 2004). Green et al. (1999) argue that this phenomenon is related to the dopaminergic antagonism created by antipsychotic drugs in the reward pathway in mesocorticolimbic neurons. High-potency antipsychotics have a stronger antagonistic effect, which is thought to increase the quantity of substance taken to reach the satisfaction felling (Martinotti et al. 2008).

Brown et al. (2002) investigated the efficacy of quetiapine in patients with bipolar affective disorder with comorbid cocaine dependence or substance abuse. They

reported that quetiapine alleviated mood symptoms and decreased cocaine craving, but that there was no difference in the amount of money spent for the substance used, the frequency with which the substance was used, and the frequency of positive urine test results for the substance used. In another study, patients diagnosed with bipolar I, bipolar II, schizoaffective disorder, and borderline personality disorder, in addition to alcohol dependence, were given a daily quetiapine dose of 300-800 mg for 16 weeks following detoxification treatment. At the end of the study it was observed that quetiapine decreased the psychiatric symptoms that accompanied alcohol consumption and craving (Martinotti et al.,2008).

Other studies focused on the use of quetiapine in patients with alcohol and substance use disorders, but no other comorbid psychiatric disorder. Sattar et al. (2004) gave 50-300 mg/day of quetiapine to 9 patients with alcohol and substance dependence (cocaine and methamphetamine), in addition to antidepressant and anxiolytic treatment for such complaints as anxiety and sleep withdrawal. The researchers reported that 1 patient could not tolerate the treatment because of increased anxiety, but that anxiety and sleep withdrawal decreased in the other 8 patients. In a 6-week study conducted to evaluate the efficacy of quetiapine in cocaine-addicted patients without a psychotic disorder, 22 patients received 300-600 mg/day of quetiapine. Some of the patients could not finish the study because of quetiapine's sedative effect. In particular, during the first week of the study a significant decrease in cocaine craving was observed and patients reported that the quantity of cocaine use decreased (Kennedy et al. 2008). Pinkofsky et al. (2005) conducted a study with patients that were being treated for opioid dependence, and every 4 hours gave them one or two 25-mg quetiapine tablets,. According to the results, 79 of the 107 patients that completed the study reported a decrease in opioid craving, 52 patients reported decreased anxiety, 24 reported decreased somatic pain, 22 reported a decrease in sleep withdrawal, and 14 reported increased appetite due to the use of quetiapine. The researchers noted that 4 patients discontinued quetiapine treatment because they did not benefit from it and 7 patients stopped because they could not tolerate the side effects.

A common theme in the studies summarized above is that quetiapine can be used in the treatment of substance use disorders. This suggestion brings to mind the abuse and dependence possibility in the use of quetiapine; and also there is a growing body of research that reveals these kinds of case reports in the literature.

Data Related to the Possible Quetiapine Misuse and Dependence

In the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), substance dependence criteria include behavioral (obtaining and using the substance for a long time, failing to fulfill personal and social obligations because of substance use, continuing substance use despite damages and several attempts to quit) and physical (evidence of tolerance and withdrawal when the substance is nor taken) characteristics. On the other hand, substance abuse is defined similarly to substance dependence in terms of the behavioral problems, but does not include the physical dependence criteria. In both conditions, the symptoms should have occurred during the last 12-month period and caused clinically severe deterioration (American Psychiatric Association 1994).

When evaluated in terms of DSM IV criteria it is noteable that quetiapine abuse and dependence were first reported among prisoner populations. In the Los Angeles County Jail, which is referred to as the "world's biggest mental health institution", it is reported that approximately 30% of prisoners pretend to have a severe psychiatric disorder by reporting symptoms (hearing noises, having paranoid thoughts) in order to get quetiapine (Pierre et al. 2004). This is an important point, although the prevalence of this kind of behavior is not known.

Research revealed that quetiapine is referred to in the street language used by substance-dependent individuals by such names as "seroquel", "quell", or "susie-Q", and that it is called "baby heroin" by prisoners (Reeves and Brister, 2002; Waters and Joshi, 2007; Hanley and Kenna, 2008; Keltner and Vance, 2008). In Turkey, patients with substance dependence and their doctors report that one of the street names of quetiapine is "yellow lake." In addition, a foreign rap song mentions one of the commercial names for quetiapine among the substances that might cause dependence (Keltner and Vance 2008).

Quetiapine is not considered a substance that causes dependence and its use is not under control. Hussain et al. (2005) reported that quetiapine dependence among prisoners might be more widespread than is thought, because obtaining other substances that can cause dependence is more difficult. The fact that quetiapine is used in the treatment of anxiety and sleep deprivation due to substance withdrawal, which is frequently seen among prisoners, is suggested to be another reason. Published reports on quetiapine abuse will be briefly explained below. Diagnoses of the cases and the characteristics of quetiapine use are summarized in Table.

A case report published in 2005 tells of a 34-year-old woman diagnosed with multiple substance dependence (alcohol, heroin, and cocaine) and borderline personality disorder that had attempted suicide more than once time dissolved two 300-mg quetiapine tablets in water, which she then boiled and injected. The patient reported that she slept for 12 hours and didn't have euphoric, dysphoric, or any other effects, except for sedation (Hussein et al. 2005). Another report on the intravenous use of quetiapine presented a 33-year-old male patient with multiple substance dependence (cocaine, alcohol, heroin, and benzodiazepine) that presented to an emergency department for detoxification and rehabilitation. The patient reported that he steals quetiapine prescribed for his wife (400-800 mg/day), powders it and mixes it with cocaine, dissolves it in water, filters it through a bandage, and then injects it. The researchers noted that the patient used quetiapine in this way in order to experience hallucinogenic effects (Waters and Joshi 2007).

It is known that quetiapine is used intranasally, as well as intravenously. A case report by Morin (2007) revealed that a white powder was found in the room of a 28-year-old female patient diagnosed with bipolar schizoaffective disorder, multiple substance abuse (alcohol, cocaine, ecstasy, lysergic aside diethylamide [LSD], weight loss pills including ephedra, and some other drugs described as "sedative" by the patient), tobacco dependence, and personality disorder. The patient intranasally took smashed aspirin and quetiapine (given to her as a part of her treatment) because of the sedative effect of quetiapine. Pierre et al. (2004) also report that among the prisoners of the Los Angeles County Jail, some people use quetiapine intranasally.

Pinta and Taylor (2007) report that quetiapine causes seeking behaviors observed in substance use disorders. It is reported that a prisoner with opioid dependence and hepatitis C infection that was taking 800 mg of quetiapine and 0.9 mg of clonidine because of generalized anxiety disorder reacted and could not adapt to the reduction of quetiapine use, when his doctor wanted to gradually discontinue quetiapine treatment because of its possible effects on the patient's liver. The patient attempted to obtain quetiapine from other prisoners when quetiapine treatment was terminated. In addition, when quetiapine treatment is withdrawn, some prisoners that previously used quetiapine react to the point of suicidal attempts (Pinta and Taylor 2007).

In a study by Inciardi et al. (2007) on the abuse of prescription drugs, they present a cased that reported taking 4 "seroquel", 3 "lilly (olanzapine)", 2 "bar" (2 mg of alprazolam), alcohol, marihuana, and cocaine at the same time, having a "perfect" night. This report brings to mind that the use of antipsychotic drugs in combination with substances causing dependence started to be a common behavior.

Reeves and Brister (2007) presented 3 cases that they consider examples of quetiapine abuse. The first case was a 49-year-old male patient with a history of alcohol dependence, and alprazolam and diazepam abuse. The treatment of substance abuse started while the patient was in prison, but when the patient was released on probation he reported having withdrawal symptoms. In response, the patient began to obtain quetiapine from his friends in order to sleep, knowing of its sedative effect and that it cannot be identified in urine. After a short while he began to take one 800-mg dose of quetiapine each night, but his complaints of sleep withdrawal, irritability lasting all day, anxiety, and headache appeared when he couldn't obtain quetiapine. The patient then presented to a clinician and insisted on being prescribed at least 400 mg/day of quetiapine.

The second case was a 23-year-old male patient hospitalized because of benzodiazepine dependence. His detoxification treatment started with lorazepam, but the patient consistently asked the doctors to give him quetiapine because he heard that quetiapine is good for withdrawal symptoms. Then patient then began to steal quetiapine from his schizophrenic girlfriend and other patients that used quetiapine in order to use and sell it. It was noted that the patient used quetiapine when he couldn't obtain benzodiazepine and when he felt anxious and uncomfortable, he sometimes took 1000-1200 mg of quetiapine in a single dose, and he sometimes took up to 2400 mg/day. The patient reported that in terms of its calming effect, 200-300 mg quetiapine was equal to 1 mg of clonazepam.

The third case was a 39-year-old male patient with bipolar affective disorder. This patient was treated with quetiapine, but presented to a psychiatric clinic with complaints of increased flow of thoughts, grandiose delusions, and agitation, and insisted on being prescribed 800 mg d^{-1} quetiapine. The researchers reported that the patient had been successfully treated with 400 mg/day quetiapine, but that the patient confessed he consumed the entire prescribed dose in a short time because he exceeded the dose suggested to him, and related his complaints to not being able to find anymore quetiapine. His treatment medication was changed to aripiprazole,

which does not have a sedative effect, but although his symptoms were controlled, the patient consistently expressed that he did not like the new drug and wanted to take quetiapine instead (Reeves and Brister 2007).

Murphy et al. (2008) presented a 29-year-old male schizophrenic patient treated with 600 mg/day (single dose) quetiapine that presented to a psychiatric emergency department with complaints of sleep disturbance because he thought that the police were electronically monitoring his testicles. The patient did get some sleep when he was medicated. The next day at his assessment it was learned that the patient did not have any symptoms related to a psychotic disorder, but that he had been obtaining high doses of quetiapine from different sources to use and sell. The researchers warned doctors about people that present in order to be prescribed quetiapine by describing psychotic symptoms (Murphy et al. 2008).

In Turkey, Evren et al. (2009) report 3 cases they thought might have abused quetiapine that were followed-up at the Alcohol and Drug Addiction Treatment and Research Center (AMATEM) of *Bakirköy* State Hospital for *Mental* and Neurological Diseases. The first case was a 32-year-old male patient diagnosed with heroin, marijuana, benzodiazepine, and alcohol abuse, as well as epilepsy, which was treated with diazepam, an analgesic, an antiemetic, and an antidiareic to control withdrawal symptoms, in addition to epilepsy treatment with sodium valproate and lamotrigine. Mirtazapine was given to the patient following his complaints of sleep withdrawal, but the patient consitantly asked the doctors for quetiapine. After being discharged from the hospital voluntarily he took quetiapine prescribed by the night doctor as an extra drug from other inpatients, powdered it and used it intranasally.

The second case presented with multiple substance dependence, including heroin, that was taking risperidone for irritability and delusions of persecution, and diazepam, analgesic, antiemetic, and antidiareic treatment for withdrawal symptoms. Because of the extrapyramidal side effects related to risperidone, the patient was prescribed 300 mg/day quetiapine, but his sleep problem continued and quetiapine treatment was changed to 200 mg/day chlorpromazine. Nonetheless, the patient insisted on being prescribed quetiapine, and the outpatient clinic records show that the patient had previously asked for quetiapine.

TABLE. Published quetiapine abuse case reports.

Author, publishing date	Patient diagnosis	Substances used together with quetiapine	Method of use
Hussain et al., 2005	Polysubstance dependence Depression Borderline personality disorder	Not indicated	Intravenous injection
Waters et al., 2007	Polysubstance dependence	Cocaine	Intravenous injection
Morin, 2007	Schizoaffective disorder (bipolar type) Polysubstance abuse Tobacco dependence Personality disorder	Aspirin	Intranasal
Pierre et al., 2007	Not indicated	Not indicated	Intranasal
Pinta et al., 2007	Opiate abuse Generalized anxiety disorder	Clonidine	Oral
Inciardi et al., 2007	Not indicated	Olanzapine, alprazolam, alcohol, marijuana, cocaine	Oral
Reeves et al., 2007	Alcohol dependence Alprazolam, diazepam abuse	Not indicated	Oral
	Benzodiazepine dependence	Not indicated	Oral
	Bipolar affective disorder	Not indicated	Oral
Murphy et al., 2008	Not indicated	Not indicated	Oral
Evren et al., 2009	Heroin dependence, Marijuana, benzodiazepine, alcohol abuse, Epilepsy	Sodium valproate, lamotrigine, diazepam, analgesic, antiemetic, antidiareic drugs, mirtazapine	Intranasal
	Polysubstance dependence	Diazepam, analgesic, antiemetic, antidiareic drugs, risperidone, chlorpromazine	Oral
	Polysubstance dependence	Diazepam, analgesic, antiemetic, antidiareic drugs	Oral

The third case was a patient with multiple substance dependence, including heroin. He repeatedly asked for a higher dose of quetiapine even though he was treated with 600 mg/day for his sleep withdrawal complaint. It is reported that the patient had requested high doses of quetiapine when he was an inpatient, although he did not have any active psychotic symptoms (Evren et al. 2009).

Except for case reports, there are no studies on the characteristics of quetiapine use among prison populations. In a Turkish study by Kaya et al. (2009), among 37 patients that were brought to the Ankara AMATEM outpatient clinic from prison and asked to be prescribed quetiapine, 21.6% developed tolerance to the drug and 40.5% obtained more quetiapine than the legal and suggested dose for treatment. It was reported that when the patients don't take the drug, 100% of them have sleep withdrawal symptoms, 70.3% exhibit nervousness, and 64.9% have withdrawal symptoms such as restlessness. As these symptoms are in line with DSM-IV substance dependence criteria, it appears that quetiapine has the potential for substance abuse and dependence.

DISCUSSION

The mechanisms described below were highlighted in studies that focused on the therapeutic use of quetiapine in substance use disorders:

1. Quetiapine provides sedation via blockage of H_1 receptors (Reeves and Brister 2007).
2. According to the self-medication hypothesis of Khantzian, people start to take substances in order to alleviate the symptoms of anxiety, and then dependence develops. Quetiapine can reduce the effect of dependence by reducing the symptoms of anxiety (Khantzian 1985; Martinotti et al. 2008).
3. The affinity of quetiapine for dopamine receptors is low, and quetiapine detaches a short time after it attaches (Morin 2007).
4. Substance-dependent patients have obsessive thoughts related to the substance they use; the antipsychotic effect of quetiapine helps to reduce these thoughts (Martinotti et al. 2008).
5. Patients with substance use disorders are also diagnosed with personality disorders; quetiapine can indirectly influence substance use by treating the psychopathology (Evren et al. 2009).

Similarly, the potential for quetiapine abuse was reported with the following explanations:

1. Quetiapine abuse is most frequently related to its sedative and anxiolytic characteristics (Pinta and Taylor 2007; Reeves and Brister 2007).
2. It is thought that the motivation for quetiapine abuse is self-medication for the symptoms of anxiety and sleep withdrawal, not the desire to get high (Pierre et al. 2004; Reeves and Brister 2007; Kaya et al. 2009).
3. The fact that quetiapine rapidly detaches from D_2 receptors may contribute to the its potential abuse, and to the lack of euphoria or dysphoria as withdrawal symptoms (Morin 2007).
4. The fact that quetiapine use is not under control and other extensively used substances that might result in dependence are difficult to obtain might lead to quetiapine abuse (Inciardi et al. 2007; Pinta and Taylor 2007).

Sedation is a frequently encountered side effect of quetiapine. Calabrese et al. (2005) report that 29.6% of patients that took 300 mg/day quetiapine and 32.2% of patients that took 600 mg/day quetiapine experienced sedation. The sedative effect of quetiapine significantly increases when consumed at high doses, especially in combination with alcohol and other sedative substances. It is posited that its sedative effect is mostly related to H_1 receptor antagonism. In addition, it is thought that antidopaminergic and anti-serotonergic effects might have a role in its sedative effect. In relation to this, it is known that quetiapine is sometimes prescribed off-label for the treatment of sleep withdrawal (Robert et al. 2005; Rowe 2007; Philip et al. 2008). The anxiolytic and sedative effects of quetiapine help to alleviate such withdrawal symptoms as anxiety, irritability, and sleep withdrawal in patients with dependence to central nervous system (CNS) stimulants or CNS-suppressive substances like alcohol and opiates. From then on, the patients might start to abuse quetiapine prescribed for treatment, which is not controlled for its use.

Researchers argue that quetiapine intranasal or intravenous abuse is more common than thought (Pierre et al. 2004; Hussain et al. 2005). Although there is no evidence supporting this view, intranasal use of quetiapine might work pharmacokinetically faster than oral use. Patients might prefer the intranasal use of quetiapine because its anxiolytic and sedative effects work faster (Morin 2007).

On one hand, using prescribed drugs in combination with illegal substances prevents the toxic side effects that might be caused by overdosing; on the other hand it helps to intensify the desired effects. An example of this is the intravenous use of cocaine together with heroin (known as a "speedball") (Waters and Joshi 2007). In a case mentioned previously in this review, it is thought that quetiapine was used instead of heroin together with cocaine (the combination of cocaine and quetiapine is known as a "Q-ball"). When the anxiolytic and sedative effects of quetiapine reduces the dysphoria developed due to the lack of cocaine in a short while, it might also create a hallucinogenic effect as reported by the use itself. The composition of the hallucinogenic effect mechanism cannot be explained (Waters and Joshi 2007).

It is noteworthy that the case reports of quetiapine abuse mostly involve patients with a substance use disorder. Only 1 case with bipolar affective disorder was observed to increasingly use quetiapine (Reeves and Brister 2007). This might be because patients with a substance use disorder use quetiapine for its sedative and anxiolytic effects in order to reduce the irritability they experience when they cannot take other substances (because they are in prison, or cannot obtain other substances). It is possible to argue that the sedative and anxiolytic effects of quetiapine (for which it is preferred in clinical settings) might be why it's used in the streets as well. These attitudes toward quetiapine are considered to be similar the abuse of anticholinergic drugs and low-potency antipsychotics such chlorpromazine and thioridazine, which occurred in the past when atypical antipsychotics were not commonly used (Pierre et al. 2004). In addition, it has been reported that some patients had to be excluded from studies because they couldn't tolerate the sedation associated with quetiapine (Kennedy et al. 2008). This finding suggests that quetiapine abuse might not always be related to the desire for sedation. In the treatment of all substance use disorders, two crucial factors are patient motivation for treatment and patient expectations of the treatment. Considering these factors, quetiapine might become a replacement substance or abuse might continue with quetiapine in patients with a low tolerance for anxiety, or expect to be away from the substance for a short time, or can't use the substance because of the conditions (being in prison, in hospital, or under surveillance because of the supervised liberty, or financial problems) they live in even though they don't expect to be treated. The cases mentioned above show that the behavioral characteristics of patients are primarily associated with substance use disorders. In the process of developing dependence, the role of the mesolimbic reward system is critical.

The mesolimbic reward system originates in the ventral tegmental area, and is related to the nucleus accumbens and the prefrontal cortex. The pathways in this system contain dopaminergic neurons. The concentration of extracellular dopamine increases in the brain in alcohol and substance dependence, even though it occurs via different mechanisms (Blum et al., 2000). It is clear that this mechanism is not activated in the process of possible quetiapine abuse or dependence. Nevertheless, the fact that quetiapine rapidly detaches from D_2 receptors might contribute not to have euphoria or dysphoria due to the lack of the drug, but also to the potential of quetiapine's abuse (Morin 2007).

Quetiapine abuse is increasing and this might be because clinicians prescribe fewer benzodiazepine, barbiturate, and stimulant drugs for substance dependence treatment and in prisons because of their addictive characteristics. The increase in quetiapine abuse might also be related to increased use of quetiapine because of its anxiolytic and sedative effects, and because it is thought that it won't result in dependence. In order to evaluate this it might be useful to track quetiapine's off-label prescription use for the treatment of the symptoms of anxiety, irritability, and sleep withdrawal over time.

CONCLUSION

Quetiapine is a drug approved by the FDA (Food and Drug Administration) for use in the treatment of schizophrenia, acute mania, and bipolar depression. Its effectiveness in the treatment of substance use and anxiety disorders has also been reported. It is reported that quetiapine is increasingly abused, especially by patients diagnosed with substance use disorders and by prisoners. This observation, along with the lack of evidence that quetiapine use causes abuse and dependence leaves clinicians with a dilemma concerning prescribing quetiapine to treat these groups of patients. This dilemma contains the risks of supporting the dependence of the patient, and not using a drug that can be beneficial for the patient. This review aimed to examine published reports on quetiapine abuse or dependence, and to present an overview of this subject by discussing the possible mechanisms responsible. Additional studies that focus on patients with substance use disorders that are treated voluntarily or by court order, and controlled double-blind studies involving people that have never used quetiapine are needed.

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