

Misuse and abuse of quetiapine

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Summary

Quetiapine is an atypical antipsychotic agent, frequently used in psychiatry, often for symptomatic treatment against a number of mental disorders differing from the registration indications. One of the uses is to soothe the clinical conditions caused by the use of various psychoactive substances.

The paper presents and discusses the reports of quetiapine misuse, abuse, and even mental addiction, as well as symptoms similar to the so-called discontinuation syndrome, often mixed with withdrawal syndrome occurring in the course of addiction.

Most reports concern males, and especially those with a history of other psychoactive substance abuse, and personality disorders, often in conflict with the law. Therefore, clinicians should be cautious when prescribing quetiapine to such patients.

Key words: quetiapine, abuse, addiction.

Introduction

Quetiapine belongs to the most commonly used drugs for the primary treatment and supportive symptomatic treatment (“off label”). It is estimated that 60-70% of

Work is not sponsored.

The article discusses potential mechanisms responsible for quetiapine abuse.

This is probably related to its sedative and anxiolytic activity which results in the frequent use with stimulants. Also, high affinity for the H1 receptor, as antihistamines agents causes rewarding action.

patients treated with quetiapine receives that drug for indications other than for which it is registered [1-3]. Very often quetiapine is used in the treatment of various disorders due to psychoactive substance use, including the treatment of affective and psychotic disorders associated with comorbid abuse or addiction to them [4, 5].

Misuse, abuse and dependence (psychological) of quetiapine.

Although many studies have shown a positive effect of quetiapine on the various conditions associated with substance use, there have been many reports of misuse, abuse, psychological addiction, and even addiction (dependence).

Most often reported cases are in the concepts of misuse, abuse and psychological dependence.

The cases of misuse, abuse, and specially dependence of other than quetiapine antipsychotic drugs are much rarer. In a specific population of 429 addicted to psychoactive substances American patients, 17% have used a variety of atypical antipsychotic drugs illegally or for non-medical purposes. Among these, the most popular was quetiapine (96%); other antipsychotics were rarely used: olanzapine (28%), risperidone (20%), aripiprazole (20%). In most cases, these drugs have been used to cope with withdrawal symptoms or to increase the effectiveness of alcohol or other substances, and not as a “leading” substance [6]. In populations other than addicted persons abuse the antipsychotics other than quetiapine is very rare.

Misuse

Cases of intranasal or intravenous administration of quetiapine in tablets for oral intake were described.

Pierre et al. [7] were the first to describe the behavior of prisoners who received quetiapine both orally and nasally inhaling powdered tablets. They reported that this way of use is more hypnotic and allows to quickly obtain sedation and anxiolytic effect. In one of the prisons 30% of inmates simulated psychotic symptoms (auditory hallucinations, paranoid delusions) to swindle quetiapine [7].

The case of 28-year-old woman suffering from schizoaffective disorder and personality disorders, who used various psychoactive substances and alcohol was described. She accumulated quetiapine tablets during hospitalizations and then she received them intranasally in the form of powder. She stated this increased sedative effect of the drug [8].

Hussain et al. [8] published a report of a 34-year-old women who were repeatedly sentenced to imprisonment for possession of illegal substances. She was diagnosed with borderline personality and the dependence of many psychoactive substances and also with two depressive episodes in the past. Because of sleep disorders, impaired impulse control, irritability and depressed mood she received 600 mg of quetiapine in

the evenings. Once she had dissolved tablets in water, boiled it and filtered through the cotton wool, and then injected this preparation intravenously. She fell asleep before she could remove a syringe from a vein. Then she described that she “experienced the best sleep in her life”. She had no more impressions or experiences. Earlier the same patient experimented with intranasal use of quetiapine [9].

In addition, the cases of using quetiapine in combination with other psychoactive substances, such as cocaine, cannabinoids or opioids, mainly in order to intensify the sedative and anxiolytic effect were reported. Such mixtures are administered in a different way: orally, intranasally or intravenously. Quetiapine applied intranasally or intravenously probably acts faster than the one taken orally, although there is no studies concerning this subject. During such an administration the hepatic metabolism is skipped and a higher dose of the drug quickly gets to the CNS. For this reason, this way of administration may be preferred by abusers.

Waters and Joshi [10] presented the case of a 33-year-old man dependent on a number of psychoactive substances (cocaine, heroin, alcohol, benzodiazepines), who stole his wife’s quetiapine, crushed it, combined with cocaine and water, warmed it and filtered through cotton wool into a syringe and took it intravenously. Combination of quetiapine and cocaine resulted in the expected hallucinogenic effect, he argued.

Evren et al [11] reported a case of a 32-year-old man addicted to heroin, marijuana, benzodiazepines and alcohol, suffering from epilepsy, which was treated with: diazepam, valproic acid, lamotrigine and drugs used in withdrawal syndrome. Because he complained about sleep disturbance mirtazapine was added, but he constantly insisted on quetiapine receiving. After discharge from the hospital he powdered and nasally took quetiapine. He extorted the drug from another patient [10].

Another unique way of taking quetiapine is its smoking. A case of a patient, who preferred marijuana, but used other substances was described. He inhaled crushed tablets of quetiapine mixed with an ounce of marijuana 1-2 times weekly [12].

Inciardi et al. [13] described the case of a person who was taking 4 tablets “Se-roquel” (quetiapine), 3 tablets of “Lilly” (olanzapine), and 2 tablets of “Bars” (2 mg alprazolam), alcohol, marijuana, cocaine at the same time to experience the “perfect night”.

In addition to case reports also the paper from Canada was published where 74 participants of methadone program were asked the questions [14]. It was found that 80% of respondents at least once in their lives have used quetiapine, for 37% it was prescribed, 21% were using it without medical recommendations, and 42% were taking medication for both the medical recommendations, and from illegal sources. 75% manifested at least one form of misuse of the drug, mainly using the quetiapine with another psychoactive substance (28%), two people (4%) reported using it to interact with methadone obtained in program and next two people (4%) have used it intranasally. Half of the participants of substitute treatment had contact with quetiapine

before and half after the therapy has started. Abusing of sedative- hypnotic drugs before the program increased the risk of misuse of quetiapine more than eight times. This phenomenon was not observed in case of prior use of other substances. The reasons for prescribing quetiapine in this group were mainly sleep inducing or anxiolytic effect (87%), positive effect in withdrawal syndrome (7%) and treating psychosis or bipolar disorder (4%).

Quetiapine abuse

The first case of abuse of quetiapine was described in 2008 [15]. 100 mg/d of quetiapine was prescribed to 48-year-old man addicted to alcohol and benzodiazepines for 15 years. After a few weeks he increased by himself the daily dose to 1000 mg. He took it with clonazepam sometimes, claiming that clonazepam itself is a poor anxiolytic and has a limited impact on mood disorders and irritability, but taken with quetiapine gives “ perfect results”. He also noticed that quetiapine increases the sedative effect of clonazepam.

Evren et al described two patients abused quetiapine [11]. The first of them was addicted to many substances and received risperidone, diazepam, analgetics and other medicines to relieve withdrawal syndrome. He reported extrapyramidal symptoms so risperidone was changed to 300 mg of quetiapine. The drug was changed once again to 200 mg of chlorpromazine because of persisting sleep disorders. The patient, however, insisted on the treatment with quetiapine. In his medical history there was a note that he previously had demanded quetiapine. The second patient was addicted to heroin and other substances. He was treated with 600 mg of quetiapine because of sleep disorders. After discharge, he constantly demanded higher doses of quetiapine although there was no psychotic symptoms.

Three more cases of quetiapine abuse were published in study of Reeves and Brister [16].

The first case was a 49-year-old man with alcohol dependence, misusing alprazolam and diazepam. He was sentenced to prison were the withdrawal of these substance had started. So he started to buy quetiapine from inmates, knowing that it has a positive effects on sleep and cannot be detected in the routine urine tests. Soon he was receiving 800 mg of quetiapine per day, and in the days when he could not get it, he reported sleep disturbances, irritability, anxiety, headaches. He insisted on the implementation of 400 mg/d of quetiapine per day [16].

The second case was a 23-year-old man hospitalized because of the addiction to benzodiazepines. Detoxification was started with lorazepam, but the patient constantly insisted on giving him a quetiapine, because he'd heard that the drug reduces the severity of symptoms. The patient began to steal quetiapine from his girlfriend suffering from schizophrenia and from other patients using this drug. He received quetiapine when he could not get benzodiazepines, or was anxious. He was receiving 1000-1200

mg quetiapine per dose, up to 2400 mg daily. He said 200-300 mg of quetiapine had the same effect as 1 mg of clonazepam [16].

The next described case was a 39-year-old man suffering from bipolar disorder. He was treated with quetiapine 400 mg/day. He came to the hospital claiming intensification of manic symptoms and insisting on increasing the daily dose of quetiapine to 800 mg/d. He admitted that the previously prescribed dose he received in a short time. The treatment was changed to aripiprazole, but the patient constantly demanded previous drug [16].

Another similar report comes from the Netherlands [17]. Two men were addicted to alcohol, one of them also to cocaine and the second one to marijuana, both were diagnosed with borderline personality disorder and increased the prescribed dose of quetiapine from 200 mg/d to 800 mg/d by themselves.

Fisher and Boggs [18] reported a single case of a man addicted to alcohol and with gambling problem. He received the treatment with quetiapine and then he increased the daily doses by himself (the maximum dose was not specified in the publication). Contrary to his expectations, the large doses of quetiapine resulted in irritability and insomnia: he felt only sleepy so he increased the dose of quetiapine to obtain a soporific effect.

Addictive using of quetiapine (psychological dependence)

In the literature, the cases of people addicted to quetiapine are also described (psychological dependence). Murphy et al. [19] presented a case of a 29-year-old man who came to the emergency room claiming that he suffered from schizophrenia and was treated with quetiapine. He asked for a prescription for this drug. He was admitted to the hospital, and received his (as reported by him) evening dose of 600 mg of quetiapine. Then he fell in deep sleep. The next day psychiatric examination did not confirm the presence of psychotic or mood disorders. Patient said that in recent months he wheedle quetiapine from different doctors, but also dealed it [19].

Another case was a 39-year-old prisoner suffering from hepatitis C abusing opiates in the past. He was receiving 800 mg of quetiapine and 0.9 mg of clonidine every evening. Because he was not mentally ill and had liver damage, psychiatrist decided to discontinue quetiapine. The patient did not agree and informed that he would buy the drug illegally from other inmates, as he did previously [20].

The phenomenon of phishing quetiapine for its chronic use in some prisons of U.S. took a mass character. Pierre et al described the prison, where nearly one-third of the prisoners simulate psychotic symptoms for permanent access to this drug [7].

The issue of possible dependence on quetiapine (withdrawal or discontinuation syndrome?)

The main biological symptoms of dependence are withdrawal symptoms and change (usually increase) of tolerance. There are several case reports of symptoms that occur as a result of withdrawal or rapid reduction of the dose of quetiapine.

Thurstone and Alahi described, in the year 2000, the case of a 21-year-old woman with schizophrenia treated with many drugs, including quetiapine at a dose of 300 mg/d with no improvement [21]. 20 hours after the last dose of quetiapine she experienced sweating and after next few hours, the other symptoms like dizziness, nausea, nervousness, and vomiting. Cardiovascular parameters were normal. After administration of 100 mg of quetiapine symptoms disappeared within an hour. The authors of this report called this status “a possible accident of quetiapine withdrawal syndrome.”

A similar case has been interpreted by Kim and Staab [22], as “a quetiapine discontinuation syndrome”. They described the 36-year-old patient with bipolar disorder who was receiving 100 mg of quetiapine only for sleep. Because she gained the weight the dose was reduced to half, however, as a result the next day the patient reported nausea, dizziness, headache and increased anxiety. The symptoms didn’t disappear at 75 mg quetiapine/d, but after returning to the starting dose of 100 mg/d.

A similar case of “quetiapine withdrawal syndrome” was reported by Kohen and Kremen. The 65-year-old patient was receiving 400 mg of quetiapine because of schizophrenia [23]. Since the drug was ineffective the dose was gradually reduced over a week and replaced by risperidone. Two days after discontinuation of quetiapine patient experienced nausea and vomiting, increased blood pressure and reported anxiety. The symptoms disappeared at 100 mg of quetiapine. Although the authors used the term “withdrawal syndrome”, they explained this phenomenon as a discontinuation syndrome.

The next described case was “reverse withdrawal dyskinesia associated with quetiapine” [24]. The patient was a 64-year-old man with bipolar disorder in euthymia phase, treated with lithium carbonate, valproate and 400 mg of quetiapine (for sleeping). Three days after the discontinuation of quetiapine asymmetric, uncontrolled, choreoatetic movements of the body appeared, mainly in the back and limbs muscles. Dyskinesia in the face muscles and slurred speech was also observed. When quetiapine was introduced then gradually, dyskinesia disappeared completely after 5 days. In this case, the term “withdrawal” meant only the situation of drug withdrawal, not a withdrawal syndrome.

Ahmad and Prakash [25] described the case of woman with schizoaffective psychosis who 2 days before the intervention discontinued 400 mg/d of quetiapine. She came to the hospital because of the sudden appearance of “reversible hyperkinetic movements” in the face and hands muscle, ataxia and incoherent speech preventing anamnesis. She was first wrongly diagnosed with an alcoholic delirium, but after finding quetiapine in the urine that drug was introduced at the dose of 100 mg, which resulted in first easing and then disappearing of symptoms.

Other authors have described patients who after discontinuation of quetiapine experienced nonspecific symptoms common in withdrawal syndromes as sleep disorders, irritability, nervousness, anxiety and headaches [16]. It should be noted that the definition of withdrawal syndrome emphasizes the need of finding the withdrawal symptoms specific to the substance. Thus, these symptoms are closer to “discontinuation syndrome” [22, 26] or “rebound symptoms”. It was found that quetiapine has the greatest potential to trigger the discontinuation syndrome in between of atypical antipsychotic drugs [26].

The case reported by Yargica and Caferova [27] refers to the 37-year-old man addicted to alcohol. 100 mg of quetiapine, venlafaxine and naltrexone was ordered to him 17 months ago. Patient first increased the dose of quetiapine by himself, and then discontinued taking the drug. This resulted in flu-like symptoms like back pain, fatigue, dysphoria, and nervousness. These symptoms ceased when after the week he began to take quetiapine again. The patient confirmed that similar symptoms appeared when he tried to reduce gradually the dose of quetiapine. It has been observed to increase the daily dose to 600-700 mg of quetiapine/d, then decreased to 300 mg/d. The attempts to replace the quetiapine with long lasting formulation was unsuccessful because the patient had not experienced the expected rapid acting of the drug (“rush”). The authors ascertained the patient had all seven symptoms of dependence according to DSM-IV, but they did not refer to the need of determining the specificity of the quetiapine withdrawal syndrome.

While in the above-mentioned cases dependence diagnosis was based mainly on symptoms considered by the authors as “withdrawal” (although they were closer to the so-called discontinuation syndrome), whereas Chen et al [28] emphasized the other symptoms described by their case. They presented the case of a 59-year-old man suffering from bipolar disorder, who, because of depressive symptoms increased quetiapine to 2,400 mg/d, zolpidem to 600 mg/d and clonazepam to 20 mg /d by himself and took it for one year. Attempts to withdraw benzodiazepines resulted in the occurrence of typical symptoms of withdrawal. He tried to control these symptoms by increasing the dose of quetiapine from 800 to 2400 mg/d, besides, quetiapine improved his mood. Attempts to reduce the dose of quetiapine resulted in heart palpitations, anxiety, nervousness and sleep disorders. Return to large doses of quetiapine caused improvement in mood, anxiety and functioning. In the hospital he was treated for depression, chronic insomnia and detoxified with valproates, mirtazapine, clozapine, clonazepam and midazolam. After the positive outcome hospitalization the patient immediately went to different hospitals, where he received a large amount of quetiapine, zolpidem and clonazepam. The authors of the reports have drawn attention to symptoms such as: the search for the substance, withdrawal symptoms (rather non-specific), increase of tolerance and impaired social functioning, which are the criteria for substance dependence according to DSM-IV-TR.

Similarly, Murphy et al [19] quite briefly described the case of a 29-year-old man treated for schizophrenia with 600 mg of quetiapine per night. He gained the drug from many sources partially trading the drug, partially using it in high doses. The researches interpreted those behaviours as: searching for the substance, compulsive use of a substance and its illegal distribution. They called this phenomenon as “addictive potential of quetiapine“.

Indirect evidence of potential for abusing quetiapine

In addition to clinical cases of misuse /abuse/ addictive use of quetiapine, the fact that quetiapine is commonly prescribed for indications other than for which it is registered (approximately 70% of all prescriptions) is striking [1-3]. This may be the result of not only versatile action on some of the common symptoms (e.g., restlessness, anxiety, insomnia), but also the result of the action similar to other substances of abuse potential.

In contrast to the psychotropic drugs of no or low potential for abuse, quetiapine got many colloquial names in addicts environments. In the U.S. the name of quetiapine, besides the brand name “Seroquel”, is “quell”, “Susie-Q”, “baby-heroin”, “Maq Ball”, “Q-Ball” [5, 10, 12, 16, 29, 30]. The latter is intravenously administered combination of quetiapine and cocaine, where quetiapine is a replacement for heroin in another, often used mixture called “speedball”. In Turkey one of the street names used for quetiapine is “yellow lake” [4]. In addition, the trade name of one of the quetiapine formulations in the U.S. is mentioned in the rap song along with other substances that cause addiction [31].

Drugs used for other than medical purposes usually have a higher price on the black market than in pharmacy. Quetiapine black market price in the United States is 3-8 dollars per one 25 mg tablet [31]. Tarasoff and Osti report that quetiapine is an easy to sell drug [32].

The objectives of the non-medical use of quetiapine

It seems that one of the main objectives of the use of quetiapine is coping with such symptoms as anxiety and insomnia [32]. Sometimes the effects surpass the expectations of doctors and patients “experience the best sleep in one’s life”, “deep sleep like a coma.”

Close to dreaming states effects of quetiapine were reported. One report describes the person who experienced hallucinogenic effects after intravenous administration of quetiapine in combination with cocaine [10].

For some people, probably mostly alexithymic, the speed of quetiapine impact on the change of consciousness (so-called “kick”, “departure”) is more important than its specific action [32, 33]. That is why administrations guaranteeing its rapid operation are preferred.

For some addicted people expected stimulatory effects is associated not only with the specific action of the substance, but also with the very act of its administration (intravenously, intranasally) [33].

Factors predisposing to misuse, abuse and dependence of quetiapine

Besides the analysis of reported cases of misuse, abuse and dependence quetiapine, there are no studies on predisposing factors. However, that is characteristic that almost all reported cases concerned people abusing other substances in the past or being addicted to them [8-10, 12, 14, 20, 27, 28].

Descriptions of cases of improper admission or abuse of quetiapine are mainly related to men [7, 9-11, 16, 20]. Another high-risk population are prisoners and persons with criminal records [7, 9, 16, 20, 30], and in some prisons it is a widespread phenomenon [7].

These observations tend to special care when prescribing quetiapine to persons mentioned above. Meanwhile, people with risk factors for misuse / abuse / addicting use of quetiapine are the group where this drug is prescribed relatively often. While the knowledge about the addictive potential of barbiturates or benzodiazepines results in their cautious prescribing, especially to addicts, quetiapine, which is an attractive alternative because of its tranquilizing and hypnotics properties, is still prescribed without thoughts about its addictive potential. It can't be excluded that patients simulate the above symptoms (or even mental illness) to swindle quetiapine.

However, people who have symptoms of discontinuation the quetiapine appear to be a different group: they are mainly those who were treated with quetiapine because of serious mental illnesses, especially schizophrenia [21, 23, 25] and bipolar disorder [22, 24]. Sometimes the discontinuation syndrome occurred at low doses of quetiapine [21] and substance seeking typical for dependence is rare [34]. Mechanisms of discontinuation syndrome seem to be different then abusing of quetiapine [21].

Attempts to explain the mechanisms of misuse and abuse of quetiapine

The most probable hypothesis is sedative / anxiolytic effect of quetiapine [15, 18, 20]. Probably because of such an action quetiapine is often combined with stimulants (e.g. cocaine, amphetamines), as it reduces the symptoms of anxiety occurring after use of those substances. Comparing to other antipsychotics quetiapine has a relative high affinity for the histamine receptor H1 and probably because of this is more frequently used without prescription then other sedative antipsychotics as olanzapine or clozapine. In rodent studies administration of antihistamines increases release of dopamine in the ventral striatum just like other addictive substances, such as cocaine or morphine. Thus, quetiapine, just as antihistamines, may have reward properties, same as psychostimulant substances [35, 36, 37]. Quetiapine has a dopaminolytic effect but comparing to other

antipsychotics it has weaker effect on D2 receptors and very rapidly disassociates from them [38]. This mechanism may indirectly explain the preferential use of quetiapine, and no other antipsychotic drugs. Other mechanisms leading to abuse are not excluded.

Suggested practical recommendations

It is recommended to continue the systematic pharmacological and clinical researches on the abuse potential of quetiapine. The scale of misuse / abuse / dependence on quetiapine is unknown, but it seems to be much more common than it is reported.

The knowledge of specific risk groups (people abusing or dependent on other substances, particularly on many substances, people with personality disorders, prisoners and men) requires special care in prescribing quetiapine [15, 39] and then monitoring possible misuse / abuse / addicting use.

On the other hand, it should be highlighted that reports on abusing quetiapine come mainly from prisons and specific groups of patients, which limits the extrapolation of these conclusions to the general population.

There are opinions that prescribing quetiapine for indications other than registered should be controlled [19, 39], and on Florida quetiapine may be prescribed only after well documented at least five unsuccessful treatment with other antipsychotic drugs [39]. Recoppa suggests that sustain quetiapine might have lower abuse potential [39].

The other opinions are less categorical. For example, Gugger and Cassagnoi do not suggest the restriction in prescribing low doses of quetiapine, but think that the knowledge that the drug is not as safe as previously reported should be spreaded [40].

Tcheremissine [41] is even more moderate. He believes that despite numerous, disturbing case reports concerning specific populations the researches on quetiapine potential for abuse are necessary and the solutions which don't limit the access for ill people to this drug should be offered.

Symptoms of discontinuation syndrome are related to different population: mainly patients chronically treated for schizophrenia and affective disorders. It should be noted, however, that the knowledge of the relatively largest potential for causing discontinuation syndrome between the atypical antipsychotics is not widespread [25]. In addition, in the presented cases, the discontinuation syndrome was atypical or non-specific and caused diagnostic difficulties or even errors [24], and thus delayed proper treatment.

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