
Quetiapine abuse – myth or reality?

PERSPECTIVES

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Quetiapine is increasingly being used as a sedative and hypnotic drug, especially in the treatment of addiction disorders. Some have warned against this practice. However, a review of the research literature lends little support to these warnings.

The risk of dependency limits the use of sedatives and hypnotics, especially in vulnerable patients. Antihistamines, antidepressants and antipsychotics are therefore often prescribed instead, but adverse effects limit their utility. Second-generation antipsychotics have significantly fewer parkinsonian adverse effects and are increasingly used. This applies to quetiapine in particular. A number of articles in the Journal of the Norwegian Medical Association are warning against this increase (1, 2). These drugs have been approved for treatment of mood disorders and psychoses, but the dosages indicate its use for insomnia and other sleep disorders (2). In spite of a call for a reduction in the prescribing of antipsychotics, especially to older people, the prescribing of quetiapine is increasing (3). Some recent reports have given rise to the suspicion that this increase may be due to patients who actively want such a prescription (4).

Quetiapine in the treatment of addiction

Patients with addiction disorders frequently suffer from agitation, anxiety, depression and not least insomnia. Comorbid afflictions such as anxiety disorder and depression are common, due to genetic issues as well as various stresses. However, benzodiazepines and z-hypnotics reinforce the intoxicant effects and can trigger as well as reinforce the tendency to use intoxicants. Furthermore, they increase the risk of complications, including the risk of a fatal overdose. Many patients refuse to use pharmaceutical drugs that have no potential for abuse, for reasons including adverse effects. Second generation antipsychotics are generally better accepted by the patients, and in recent years quetiapine has in particular been prescribed.

Risk of abuse?

Reports from a number of countries show that the use of quetiapine is increasing and that a considerable proportion of the prescribing is off-label (5–8). The question is what this trend reflects and how it should be assessed. The terms *abuse* and *misuse* are often used in this literature. One report uses the term *recreational abuse* (5). Evoy and colleagues use the term *abuse-related events* (7). However, these terms are not defined in terms of diagnostic criteria for addiction disorder, but are based either on their use outside the approved indication or on various criteria for hospitalisation due to poisonings or other crises. Intoxication and detoxification problems are barely described, if at all. Individual reports describe pills being crushed for inhalation or injection, and some case histories describe dosage escalation and problems with dosage tapering, but it is difficult to ascertain whether this is due to an increase in problem intensity or insufficient effect. The evidence for risk of abuse of quetiapine is generally rather weak, given that heavily addicted substance abusers tend to try out many different drugs. Moreover, problems with dosage tapering are common in the use of all types of psychotropic drugs such as antidepressants and antipsychotics.

The key question is therefore whether atypical antipsychotics are sought after because of their euphoriant effects. This is rarely, if ever, clinically described, and the pharmacological profile of quetiapine renders it unlikely. The reports discuss possible mechanisms with reference to the mechanisms of action and metabolism of quetiapine. This gives an impression of theorising that has not been confirmed by animal or clinical studies. These are therefore assumptions that in reality appear to be based on concerns over increased use. The articles do not sufficiently distinguish between use outside the approved indication on the one hand and abuse on the other. If the use and dosage increases are justified by a reduction in difficulties and symptoms, this alone does not constitute abuse.

Increased mortality from the use of quetiapine?

A number of studies refer to increased mortality from the use of atypical antipsychotics, particularly quetiapine. A large Finnish registry study of mortality during long-term treatment of patients with schizophrenia with eleven years of follow-up is frequently cited. This study found that quetiapine was associated with slightly elevated mortality when compared to other atypical antipsychotics (9). The increase in mortality was due to an increased risk of suicide with the use of quetiapine, while cardiovascular mortality was the second lowest in this group. It is uncertain whether the increased incidence of suicide can be linked to the drug-based therapy, and in our opinion this study cannot be taken as evidence that quetiapine is associated with a higher mortality risk. The article's message is also another, namely a recommendation to use clozapine as less problematic than other relevant drugs. In a recent study from Finland (10), with overlapping study populations and 20 years of follow-up, the ranking of quetiapine among the other antipsychotics changes in terms of both cardiovascular and total mortality. In this study there was no difference in suicide risk among users of quetiapine and patients who were not undergoing drug-based therapy.

More adverse effects?

The most common adverse effects from the use of atypical antipsychotics are weight gain, increased triglyceride level and possibly a higher prevalence of diabetes, endocrine disturbance and cardiac complications with effects on cardiac rhythm and blood pressure. The adverse effects are primarily associated with high dosages, and are common in antipsychotic therapy. When used off-label, dosages are normally low (25–100 mg/day) for some days or weeks. There is less evidence of difficulties from such use. Cates et al. found an average weight gain of 4.2 pounds (1.9 kg) in psychiatric patients who were prescribed an average of 109.3 mg of quetiapine for insomnia in addition to other antipsychotic treatment (11). A similar study showed a weight gain of 11 pounds (approximately 5 kg) after the use of up to 100 mg of quetiapine per day for one year (12). This may indicate that quetiapine accounts for a certain

tendency towards weight gain, which is also found in the use of other antipsychotics. A comprehensive study comparing the problems inherent in the use of various types of atypical antipsychotics, based on a database of poisonings in the United States, gives little indication of specific risks (5). There was a somewhat increased tendency towards reduced alertness and a somewhat reduced tendency towards dystonia in connection with quetiapine intoxication when compared to other antipsychotic drugs. However, the similarities predominate. Nor was the severity of the intoxication any worse in case of quetiapine: 73.4 % of the intoxications were deemed to carry little medical risk and 24.6 % were considered moderately hazardous. Hazardous conditions were identified in 2 % of the cases of quetiapine intoxication. This is somewhat below the average for all antipsychotic drugs.

How useful is quetiapine in the treatment of sleep disorders?

Debernard et al. state that quetiapine is not a sleeping pill (2). As a first-line treatment for primary insomnia, this is undoubtedly correct. A large-scale review of the benefit of quetiapine for insomnia concludes that in light of the adverse effects, such use is unwarranted (13). This applies to all atypical antipsychotics (14). To be sure, some studies point out desirable effects for certain types of sleep disorders, but these studies are methodologically weak. Studies that include placebo-controlled effect on sleep lend little support to the use of quetiapine for insomnia, but suggest an effect in those who also suffer from obsessive-compulsive disorder and generalised anxiety (15).

The neurobiology behind sleep and sleep mechanisms is complex, and mental disorders affect sleep in various ways. The effect of drugs, e.g. quetiapine, can vary from one patient to another. The benefit for primary insomnia can be real in cases of complex conditions. For example, quetiapine has a separate indication as supplementary treatment for depressive disorders (16). A comprehensive review of the benefits and difficulties associated with the use of all registered atypical antipsychotics showed that their benefit varied somewhat between the different formulations (17). Quetiapine was found to be more useful than the others for generalised anxiety, but not for other conditions. Our assessment is that quetiapine might be attempted for sleep disorders or agitation when the use of benzodiazepines and z-hypnotics is undesirable.

Norwegian experiences

Data from the Norwegian Prescription Registry show that 5 183 persons were prescribed with quetiapine in 2005. In 2018, this number had risen to 63 125 persons (18). Thereby, the one-year prevalence had increased to 1.2 %. These figures also include treatment of psychoses and affective disorders, but the increase is nevertheless considerable. However, no reports of usage problems have been submitted by the departments for addiction treatment. The

medical advisor at the Emergency Addiction Services and Detoxification, Oslo University Hospital, has on request reviewed the department's clinical experience and concluded that the department has not registered any increased prescribing of or demand for quetiapine. In exceptional cases the department has encountered patients who have been prescribed with, or despite regular prescribing have used 'supratherapeutic' doses, but they have no information on patients having obtained quetiapine from others (P. Krajci, personal communication).

The heads of units that provide drug-assisted rehabilitation convene twice annually to discuss experiences. At the last session (2–3 December 2019) only one of a total of twenty units reported having encountered a wish for increased dosage. All the others reported exclusively problem-free, though often moderately beneficial use. The LASSO programme (drug-assisted harm-reducing substitution treatment in Oslo), which provides a low-threshold option for persons with addiction disorder in central Oslo, does not know of any patients who have requested this drug. This suggests that there is little demand for it in the central Oslo drug scene.

Norway has relatively high overdose mortality. 95 % of the autopsies after such deaths take place at the Department of Forensic Medicine, Oslo University Hospital. Its annual statistics provide information about the findings (19). The number of deaths where antipsychotics were detected increased considerably from 2009 to 2015, but not in subsequent years. In 2018 a little more than 2 000 investigations were carried out, and intoxicants or pharmaceutical drugs were detected in somewhat more than 1 500 of these. Olanzapine was found in 3 % and quetiapine in 4 % of the examinations (H.M. Edvardsen, Department of Forensic Pathology and Clinical Forensic Medicine, Oslo University Hospital, personal communication). In a large-scale Nordic study from 2012, quetiapine was not deemed to be the main intoxicant in any of 194 cases of overdose deaths in Norway. The substance was later detected in seven persons (3.6 %), but it was not known whether this was due to prescribed treatment (20).

Conclusion and recommendations

We cannot see any evidence that the increased use of quetiapine is due to increased abuse or addiction to this drug in Norway. However, like other atypical antipsychotics, the drug can cause serious intoxication, and it has metabolically adverse effects indicating that its use should be restricted to necessary and useful treatment. Quetiapine is approved for treatment of schizophrenia and bipolar disorders, but its use outside the approved indications has increased, for example in treatment of addiction, sleep disorders and agitation when the use of benzodiazepines and z-hypnotics should be avoided or restricted. Quetiapine is also used to support tapering and withdrawal from benzodiazepine addiction. Such treatment should be undertaken over a shorter period of time and with lower dosages, and its use should be assessed against its clinical benefit and in light of the problem that even lower dosages can result in weight gain and elevated triglyceride levels.

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