



Tidsskriftet
DEN NORSKE LEGEFORENING

Quetiapine is not a sleeping pill

PERSPECTIVES

KAREN ASTRID BOLDINGH DEBERNARD

Karen Astrid Boldingh Debernard, PhD, Cand. pharm. is a senior adviser at RELIS (Regional Medicines Information and Pharmacovigilance Centre), Department of Clinical Pharmacology and the National Centre for Epilepsy, Oslo University Hospital.

The author has completed the ICMJE form and declares no conflicts of interest.

JOACHIM FROST

Joachim Frost, PhD, is a specialist in clinical pharmacology and senior consultant at the Department of Clinical Pharmacology, St. Olavs Hospital, Trondheim University Hospital.

The author has completed the ICMJE form and declares no conflicts of interest.

PÅL-DIDRIK HOFF ROLAND

E-mail: didrik@relis.no

Pål-Didrik Hoff Roland, Cand. pharm, is a medicines adviser at RELIS (Regional Medicines Information and Pharmacovigilance Centre), Department of Clinical Pharmacology, St. Olavs Hospital, Trondheim University Hospital.

The author has completed the ICMJE form and declares no conflicts of interest.

Use of the antipsychotic drug quetiapine to treat sleep disorders has become widespread, also in Norway. Its efficacy is poorly documented, and even low doses may have substantial side effects. There is thus reason to warn against prescribing quetiapine for sleep.



Illustration: illustratorene.no / Marius Pålerud

Quetiapine is a second-generation antipsychotic approved for treatment of schizophrenia and bipolar disorder and as supplementary treatment for depression. The recommended dose for these indications is 300–800 mg per day. Drowsiness is a very common side effect (>10 %) of the drug. In recent years prescribing of quetiapine in doses of 25–100 mg to treat insomnia has increased (1, 2). This practice has also become widespread in Norway, including to children, adolescents and elderly people. This has become apparent, for example from questions put to the Regional Medicines Information and Pharmacovigilance Centre (RELIS). A new Norwegian study for the period 2004–2017 showed that the median prescribed daily dose of quetiapine in Norway is less than 100 mg, and that only some 4 % of users received doses and reimbursement consistent with the use of quetiapine for an approved indication (3).

Quetiapine and sleep

Despite widespread use of low-dose quetiapine for insomnia, the efficacy and safety for this indication is poorly documented by clinical trials (4–6). Only one randomised trial of its efficacy for primary insomnia has been conducted, on 13 patients (7). The results were inconclusive. An open, non-controlled study over six weeks with 18 patients with primary insomnia showed an improvement for some of the subjective sleep parameters (Pittsburgh Sleep Quality Index), but the time to sleep onset was not reduced (8).

In several studies of quetiapine use in psychosis, bipolar disorder or depression, the effects on sleep were also investigated (9, 10). It is difficult to distinguish between the positive effects of treatment of the primary disorder and on concomitant sleeping problems, but it was seen in these studies that quetiapine can also have a negative effect on sleep in patients with schizophrenia (10).

Three review articles from the years 2014–2018 all conclude that it is not advisable to use quetiapine for insomnia, mainly because of lack of documentation (4–6). The first of these concludes that the risk-benefit profile for use against insomnia is disadvantageous even for patients with another indication for using quetiapine (4).

It is assumed that central histamine H₁ receptor blockade, and to a lesser extent alpha-1-antiadrenergic and antimuscarinergic properties, play an important part in the sedative effect of quetiapine (11, 12). It is estimated that almost 100 % of the H₁ receptors and over 50 % of serotonin 5HT_{2a} and dopamine D₂ receptors are blocked by use of 50 mg quetiapine (12). In other words, there is evidence that quetiapine exerts an effect on several receptor systems even in low doses.

In studies of quetiapine in patients with schizophrenia, where higher doses are used, it is found that drowsiness as a side effect does not increase much with the dose, but most users find that they develop tolerance, so that sedation is less pronounced when quetiapine is used for several weeks (10). It seems reasonable that this also applies when quetiapine is used for insomnia. The development of tolerance is also a known effect of sedating antihistamines, which also have been used as sleeping aids. This use of inadequately documented drugs with an effect on many receptor systems for insomnia is not new in Norway, and has also previously been discussed in the Journal of the Norwegian Medical Association (14).

Side effects of using low-dose quetiapine

There is considerable risk of side effects when quetiapine is used even in low doses. Weight gain and metabolic disorders, including an increase in triglycerides, have been reported for low doses of quetiapine (15–17). Daytime sedation ('hangover') is frequently reported (7–9), (15–17). Among other observed side effects of low-dose quetiapine are restless legs, akathisia, dry mouth and impaired attention (9, 15).

«We know of no guidelines that recommend quetiapine for treating insomnia»

There are no studies with observation times of more than two weeks, so the long-term effect of low-dose quetiapine treatment is unknown. Dose escalation has been reported when quetiapine is used for primary insomnia, and many patients report problems with discontinuation of the drug after low-dose use (13). There is also evidence suggesting that quetiapine has a potential for abuse (20).

Quetiapine and guidelines for treatment of insomnia

In cases of acute insomnia, treatment with drugs may be helpful. Traditional hypnotic drugs (z-hypnotics and some benzodiazepines) have an approved indication for short-term use (<2–4 weeks) and should be the drugs of choice. However, the development of tolerance and risk of dependency restrict the use of these drugs over time, and there is no good documentation of the efficacy of hypnotics for chronic sleep problems. In cases of chronic insomnia, other treatments are recommended, such as sleep hygiene advice and cognitive behavioural therapy for insomnia (CBT-I). Up to 80 % have been shown to benefit from this treatment (21, 22).

We know of no guidelines that recommend quetiapine (or other antipsychotics) for treating insomnia. Norwegian national recommendations express concern and advise against the increased use of antipsychotics for insomnia (22). European and American guidelines state that quetiapine is not recommended for insomnia because of inadequate documentation and considerable side effects (23, 24). The Norwegian electronic physicians' desk reference (NEL) and British recommendations (BMJ Best Practice) do not mention quetiapine in connection with sleeping problems (25, 26). UpToDate, a US point of care

reference work for doctors, only mentions quetiapine for insomnia for patients with a substance abuse problem, and warn against lack of documentation and substantial risk of side effects (27, 28).

The European Medicines Agency (EMA) conducted a harmonisation of the summary of product characteristics for quetiapine in Europe in 2014. Insomnia is not an approved indication in either Europe or the USA (29, 30).

Lack of documentation and approval

Our impression is that low-dose quetiapine is used as an alternative to hypnotics with dependence potential. This has also been mentioned previously in the Journal of the Norwegian Medical Association (31). We also find that low-dose quetiapine is prescribed for patients whose racing thoughts and brooding make falling asleep difficult, also in child and adolescent psychiatry. The thinking behind this use of quetiapine is apparently to induce a 'slight antipsychotic effect' to curb this. It is important to be aware that the efficacy documentation for quetiapine applies to other indications and higher doses, and that there is no documentation from clinical trials to justify such prescription. On the contrary, there is solid evidence that quetiapine can cause substantial side effects, even in low doses.

«Doctors must be aware that by using quetiapine for insomnia, they are prescribing off-label»

There may be cases of patients with psychoses where it is advisable to choose an antipsychotic with a pronounced sedative effect, particularly in an acute phase (4, 21). However, there are no grounds to recommend adding low-dose quetiapine for sleep to other antipsychotic therapy for this patient group, especially not for a longer period of time. These are patients who already have a heavy side effect and illness burden, and increased mortality. Daytime sedation can be undesirable (7–9), and quetiapine's usefulness against insomnia has not been shown to outweigh the risk in these patients (4). Other options should therefore be considered first, also in this patient group.

Quetiapine has been extensively marketed off-label, including for insomnia, and the manufacturer, AstraZeneca, was fined for this in the USA (32). Colleagues' prescription of quetiapine for sleep-related problems may also be a factor that causes an overrating of the existing evidence base. Doctors must be aware that by using quetiapine for insomnia, they are prescribing off-label and thereby assuming a greater responsibility, not least with respect to the patient's safety.

It is our opinion that an undesirable prescription pattern has developed when the antipsychotic quetiapine is used widely to treat insomnia without the efficacy or safety of this treatment being adequately documented. Quetiapine is not a sleeping pill, and should in our view not be used as such.

LITERATURE

1. Pringsheim T, Gardner DM. Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. *CMAJ Open* 2014; 2: E225–32. [PubMed] [CrossRef]
2. Kamphuis J, Taxis K, Schuiling-Veninga CC et al. Off-label prescriptions of low-dose quetiapine and mirtazapine for insomnia in The Netherlands. *J Clin Psychopharmacol* 2015; 35: 468–70. [PubMed]
3. Gjerden P, Bramness JG, Tvete IF et al. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004–2015. *Eur J Clin Pharmacol* 2017; 73: 1173–9. [PubMed]

[CrossRef]

4. Anderson SL, Vande Griend JP. Quetiapine for insomnia: A review of the literature. *Am J Health Syst Pharm* 2014; 71: 394-402. [PubMed][CrossRef]
5. Thompson W, Quay TAW, Rojas-Fernandez C et al. Atypical antipsychotics for insomnia: a systematic review. *Sleep Med* 2016; 22: 13-7. [PubMed][CrossRef]
6. Atkin T, Comai S, Gobbi G. Drugs for insomnia beyond benzodiazepines: Pharmacology, clinical applications, and discovery. *Pharmacol Rev* 2018; 70: 197-245. [PubMed][CrossRef]
7. Tassniyom K, Paholpak S, Tassniyom S et al. Quetiapine for primary insomnia: a double blind, randomized controlled trial. *J Med Assoc Thai* 2010; 93: 729-34. [PubMed]
8. Karsten J, Hagenauw LA, Kamphuis J et al. Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial. *J Psychopharmacol* 2017; 31: 327-37. [PubMed][CrossRef]
9. Trivedi MH, Bandelow B, Demyttenaere K et al. Evaluation of the effects of extended release quetiapine fumarate monotherapy on sleep disturbance in patients with major depressive disorder: a pooled analysis of four randomized acute studies. *Int J Neuropsychopharmacol* 2013; 16: 1733-44. [PubMed][CrossRef]
10. Monti JM, Torterolo P, Pandi Perumal SR. The effects of second generation antipsychotic drugs on sleep variables in healthy subjects and patients with schizophrenia. *Sleep Med Rev* 2017; 33: 51-7. [PubMed][CrossRef]
11. Fang F, Sun H, Wang Z et al. Antipsychotic drug-induced somnolence: Incidence, mechanisms, and management. *CNS Drugs* 2016; 30: 845-67. [PubMed][CrossRef]
12. Stahl SM. *Stahls essential psychopharmacology*. New York: Cambridge University Press, 2013.
13. Cornelis C, Van Gastel A, Dumont G et al. A case of dose escalation of quetiapine in persistent insomnia disorder. *Acta Clin Belg* 2017; 72: 346-8. [PubMed][CrossRef]
14. Slørdal L, Bramness JG. Er alimemazin et egnet søvnmiddel for barn? *Tidsskr Nor Laegeforen* 2008; 128: 2194-6. [PubMed]
15. Zhornitsky S, Potvin S, Motesafi H et al. Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: a systematic review of the placebo-controlled monotherapy and add-on trials. *Int Clin Psychopharmacol* 2011; 26: 183-92. [PubMed][CrossRef]
16. Williams SG, Alinejad NA, Williams JA et al. Statistically significant increase in weight caused by low-dose quetiapine. *Pharmacotherapy* 2010; 30: 1011-5. [PubMed][CrossRef]
17. Cates ME, Jackson CW, Feldman JM et al. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. *Community Ment Health J* 2009; 45: 251-4. [PubMed][CrossRef]
18. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia. *Ann Pharmacother* 2012; 46: 718-22. [PubMed][CrossRef]
19. Rittmannsberger H, Werl R. Restless legs syndrome induced by quetiapine: report of seven cases and review of the literature. *Int J Neuropsychopharmacol* 2013; 16: 1427-31. [PubMed][CrossRef]
20. Aa E, Helland A, Spigset O. Kvetiapin kan ha misbrukspotensial. *Tidsskr Nor Legeforen* 2012; 132: 1619-20. [PubMed][CrossRef]
21. Bjorvatn B. Medikamentell behandling av insomni blant voksne. *Nor Farm Tidsskr* 2016; 124: 28-31.
22. Bjorvatn B, Sivertsen B, Waage S et al. Nasjonal kompetansetjeneste for søvnsykdommer. Nasjonal anbefaling for utredning og behandling av insomni. *Søvn* 2018; 10: 12-7.
23. Riemann D, Baglioni C, Bassetti C et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017; 26: 675-700. [PubMed][CrossRef]
24. Sateia MJ, Buysse DJ, Krystal AD et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An american academy of sleep medicine clinical practice guideline. *J Clin Sleep Med* 2017; 13: 307-49. [PubMed][CrossRef]
25. Bjorvatn B, Løge I, Jost PD. Søvnløshet. *Norsk elektronisk legehåndbok*. <https://legehåndboka.no/handboken/kliniske-kapitler/psykiatri/tilstander-og-sykdommer/sovnforstyrrelser/sovnloshet/> Read 5.6.2018.
26. Lee-Chiong T, Malik V. Insomnia. *BMJ Best Practice*. <https://bestpractice.bmj.com/topics/en-gb/227> Read 19.4.2018.
27. Winkelmann JW. Overview of the treatment of insomnia in adults. *UpToDate versjon 3.0*, 2018. <https://www.uptodate.com/contents/overview-of-the-treatment-of-insomnia-in-adults> Read 10.9.2018.
28. Arnedt JT. Insomnia in patients with a substance use disorder. *UpToDate versjon 12.0*, 2018. <https://www.uptodate.com/contents/insomnia-in-patients-with-a-substance-use-disorder> Read

23.8.2018.

29. European Medicines Agency. Questions and answers on Seroquel, Seroquel XR and associated names (quetiapine). EMA/301727/2014. https://www.ema.europa.eu/en/documents/referral/questions-answers-seroquel-seroquel-xr-associatednames-quetiapine_en.pdf Read 23.4.2019.

30. U.S. Food and Drug Administration. Label information Seroquel. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020639s060s063lbl.pdf#page=48 Read 29.11.2018.

31. Gjerden P, Bramness JG, Slørdal L. Kvetiapin brukes for mye. Tidsskr Nor Legeforen 2018; 138. doi: 10.4045/tidsskr.18.0535. [PubMed][CrossRef]

32. Tanne JH. AstraZeneca pays \$520m fine for off label marketing. BMJ 2010; 340: c2380. [PubMed][CrossRef]

Publisert: 16 September 2019. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.19.0205

Received 12.3.2019, accepted 23.4.2019.

© Tidsskrift for Den norske legeforening 2022. Lastet ned fra tidsskriftet.no 18 July 2022.