A case of dose escalation of quetiapine in persistent insomnia disorder

Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine

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--Manuscript Draft--

Manuscript Number:	ACB662R2
Full Title:	A case of dose escalation of quetiapine in persistent insomnia disorder
Article Type:	Case Report
Keywords:	Quetiapine; Insomnia Disorder; Fatigue; Sedation; Tolerance
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Manuscript Region of Origin:	BELGIUM
Abstract:	Quetiapine, an atypical antipsychotic drug, is recommended for the treatment of schizophrenia and mood disorders (1,2). In addition, given its sedative effects, a low dose of the agent is also widely used in the treatment of anxiety disorders, personality disorders, substance abuse, and sleep disturbances (3). In this case study, quetiapine was the first effective drug in reducing chronic insomnia in a male patient with a long treatment history. Because its effect declined over time, in the course of two years a gradual dose increase led to a posology fifty times higher than the off-label dosage used to obtain sedation, i.e. 25-100 mg quetiapine administered once daily. This case raises awareness of the ease with which dose escalation of quetiapine can occur. The risk of side effects and, possibly, dependence and abuse underlines the importance of regular and careful patient monitoring. Given the unexpected effectiveness of the agent and the absence of side effects in the described case, we argue that in treatment-resistant insomnia a high dose of quetiapine may be justifiable in selected cases but also urge that further research on the long-term effects and potential adverse events of quetiapine for this indication is of the utmost importance.
Funding Information:	

A case of dose escalation of quetiapine in persistent insomnia disorder

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Declaration of Conflicting Interests

Claudia Cornelis and Glenn Dumont received funding for their research from Janssen Pharmaceutica N.V., Belgium. Manuel Morrens received funding for his research from Janssen Pharmaceutica N.V., Belgium, Lundbeck Belgium, and Bristol Myers Squibb Belgium and Astra-Zeneca Belgium. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of the presented case study.

Acknowledgements

The authors would like to thank Ms. Meulenbroek for her guidance and refinement of the English writing style.

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Quetiapine, an atypical antipsychotic drug, is recommended for the treatment of schizophrenia and mood disorders (1,2). In addition, given its sedative effects, a low dose of the agent is also widely used in the treatment of anxiety disorders, personality disorders, substance abuse, and sleep disturbances (3). In this case study, quetiapine was the first effective drug in reducing chronic insomnia in a male patient with a long treatment history. Because its effect declined over time, in the course of two years a gradual dose increase led to a posology fifty times higher than the off-label dosage used to obtain sedation, i.e. 25-100 mg quetiapine administered once daily.

This case raises awareness of the ease with which dose escalation of quetiapine can occur. The risk of side effects and, possibly, dependence and abuse underlines the importance of regular and careful patient monitoring. Given the unexpected effectiveness of the agent and the absence of side effects in the described case, we argue that in treatment-resistant insomnia a high dose of quetiapine may be justifiable in selected cases but also urge that further research on the long-term effects and potential adverse events of quetiapine for this indication is of the utmost importance.

Keywords: quetiapine, insomnia disorder, fatigue, sedation, tolerance

Introduction

The only approved pharmacological therapies for insomnia in Europe are benzodiazepine receptor agonists. However, in daily practice diverse other drugs such as low dose antidepressants, atypical antipsychotics or antihistamines are successfully used. It is estimated that more than 50% of all prescriptions for the treatment of insomnia in the general population concerns the off-label use of low doses of quetiapine (4). In this paper we present a case in which this agent was the only effective treatment for persistent insomnia disorder in an otherwise healthy man where cumulative increases led to an unusually high dose level. In our report we propose plausible mechanisms explaining this exaggerated but in our view understandable dose increase.

Case presentation

KU, a 40-year old Caucasian man, was referred to the Sleep Disorder Unit of the University Hospital Antwerp with complaints of persistent insomnia and mild obstructive sleep apnea (OSA). KU reported sleep-related complaints including difficulty initiating sleep, frequent early-morning awakenings with an inability to return to sleep, and severe secondary daytime fatigue. The sleep problems occurred more than three nights per week, had started during early puberty, and had seriously affected his subjective quality of life and overall daily functioning ever since. Concomitant somatic illnesses were found to be absent on the basis of medical history and clinical examination. The absence of other DSM-IV Axis 1 diagnoses was confirmed by the Structured Clinical Interview for DSM disorders (SCID-I/P) (5,6).

At first visit, baseline polysomnography (PSG) showed a mildly elevated apnoea-hypopnoea index (AHI), an elevated arousal index that did not improve with continuous positive airway

pressure (CPAP), periodic limb movements that were seldom associated with arousal indices, and a relatively low mean total sleep time. The Epworth Sleepiness Score (ESS) pointed to a mild-to-normal daytime sleepiness (Table 1). The OSA was initially treated with CPAP without any positive results. We introduced cognitive behaviour therapy for insomnia (CBTi) but KU had some reservations about applying the principles of 'time in bed restriction'. Cognitions concerning the need for more than eight hours of sleep per night remained prominent, which was understandable given that the chronic fatigue and the sleep problems (duration limited to approximately 5 hours/night) had existed for more than twenty years. KU used 87.5 mg hydroxyzine before bedtime, which improved sleep but did not alleviate the fatigue. Based on previously failed pharmacological treatments (Table 2), we decided to taper off hydroxyzine and prescribed a daily dose of 25 mg quetiapine before bedtime. The regimen increased the amount of sleep and induced limited but positive self-reported effects on daytime fatigue. The dose was gradually increased to 100 mg/day during the subsequent two months, after which KU reported approximately 8-9 hours of effective sleep per night and a major improvement of his daytime complaints. In the following months, a stable dose of 133 mg/day was reached and maintained with patient satisfaction in the absence of side effects.

After one year, the perceived effectiveness of quetiapine quickly waned. Because of the previous treatment success, we agreed with KU's request to increase the dosage with on average 70 mg/month until an effective dose was reached. After two years of frequent medical monitoring and psychotherapy, the maximum daily intake of quetiapine amounted to 1625 mg, without abnormal laboratory parameters. A second PSG confirmed an improved sleep efficiency and a meaningfully augmented sleep duration (8 hours/night). There was a reduction of the AHI to 0.7 events per hour, indicating that the mild OSA had remitted, while REM sleep duration had markedly decreased (Table 1).

In order to preclude adverse effects known for quetiapine (e.g., cerebrovascular events, neuroleptic malignant syndrome, metabolic changes, or the occurrence of suicidal thoughts and behaviours), we titrated the dose down to a slightly safer range. To date, optimal patient satisfaction was obtained without any side effects occurring with a dose of approximately 1400 mg/day, which is about fifty times the dose at which sedation normally occurs (i.e. 25-100 mg/day). A further dose reduction is complicated by the patient's reports of recurring symptoms of insomnia.

Discussion

Quetiapine is known to be an antagonist of serotonin, dopamine, histamine, and adrenergic receptors. The antagonist action on the H1-receptor induces sedation and improves subjective sleep quality at doses as low as 25 mg/day (3). Although uptitration might increase the H1-receptor occupancy and therefore theoretically fortify the agent's sedative effect, a clinical study comparing quetiapine doses of 25 and 100 mg/day in healthy volunteers did not find clinically relevant improvements on PSG with the higher dose (7). To our knowledge, however, there are no official guidelines for the safe dose range for the off-label use of quetiapine.

A plausible explanation for the excessive dosing regimen might be the development of tolerance to quetiapine's sedative effect. Despite some variation in the literature, it has been suggested that quetiapine might indeed have a potential to induce dependence (8). Tolerance for other H1-interacting agents tolerance has also been reported (9), although the effect has so far not been confirmed by objective studies (10,11).

As quetiapine is a CYP3A4 substrate, its serum concentrations might be increased by CYP3A4 inhibitors, leading to toxicity symptoms such as sedation, mental confusion, acute hypotension, syncope, dizziness, and respiratory depression, or decreased by CYP3A4 inducers, resulting in loss of the drug's efficacy. Yet, KU reported not to be taking any concomitant medications or herbal products (such as the CYP3A4 inducer St. John's wort) that might cause these drug-drug interactions. The steady-state serum concentration of quetiapine amounted to 0.3 mg/l at 13 hours after the daily dose of 1483 mg quetiapine. As this is within the safe range for the agent, i.e. 0.1-0.5 mg/l after 12 hours (12,13) an ultrarapid individual metabolism of the drug can be ruled out. However, the large interindividual variability in serum concentrations of quetiapine's active metabolite N-desalkylquetiapine, might also be of clinical importance (14,15). Further in-vitro and in-vivo studies about the role of and genetic variability in N-desalkylquetiapine's formation and elimination enzymes (eg. CYP2D6 and CYP3A5) are therefore necessary. The observed reduction in REM sleep raises the question whether high doses of the agent may paradoxically exert a negative effect on the sleep architecture, prompting dose increases. A change in the REM-sleep duration resulting from quetiapine treatment has been documented (16), yet this effect disappeared with long-term use (17), while it is uncertain whether REM-sleep deprivation affects daytime tiredness.

Ultimately, since there is growing evidence that quetiapine has the potential for dependence and misuse/abuse (18–20) we hypothesized that KU might have simulated symptoms in order to obtain more of the medication but the atypical time course marked by very careful dose increases argues against this conjecture. Undoubtedly, KU's hopelessness and preoccupation with controlling sleep time have contributed substantially to the high dosing regimen.

Conclusion

In this case report we have attempted to explain the gradual but excessive increase in quetiapine dosages in a male patient with persistent insomnia disorder. As quetiapine was the first effective treatment for this patient, we feel that its role as an alternative treatment in selected cases of insomnia merits further consideration. Our preliminary exploration of quetiapine's complex pharmacokinetic and pharmacodynamic properties, the potential adverse longer term effects on sleep architecture with higher doses, and the risks of tolerance and abuse made us conclude that its long-term use in the treatment of insomnia requires close medical follow-up and further research.

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Table 1: Polysomnography (PSG) and Epworth Sleepiness Score (ESS) performed before and after quetiapine administration

	Before start quetiapine		Quetiapine (1.625 mg/day)
PSG	**Without nCPAP**	**With nCPAP**	**Without nCPAP**
AHI	7.8	2.1	0.7
AI	28.9	20.7	10.7
TST	301	374	503
SE	75.7	87.1	91.7
REM duration	74	38	7
REM %	24.5	10.1	1.4
SWS	73.5	109.5	73.5
ESS	7	7	1

AHI (events per hour): Apnea Hypopnea Index; the average number of apnea and/or hypopnea events per hour of sleep, ranging from normal (0-4) to mild (5-14), moderate (15-29) or severe sleep apnea (≥30)
AI (events per hour): Arousal Index; average number of arousals per hour of sleep.
AI_{CPAP}: Arousal Index while using Continuous Positive Airway Pressure (average arousal frequency per hour of sleep)
TST (minutes): Total Sleep Time; actual sleep duration, e.g. the total of all REM and non-REM sleep in a sleep episode.
SE (%): Sleep efficiency; the ratio of total time spent asleep (TST) to the total amount of time spent in bed
REM sleep duration (minutes): duration of Rapid Eye Movement sleep
Proportion of REM sleep (%): Proportion of REM sleep per sleep episode (TST); usually 20-25% of TST
SWS: Slow Wave Sleep; comprises NREM sleep stages 3 and 4 which are thought to be involved in cerebral restoration and recovery in humans and the maintenance and consolidation of sleep
ESS (score): Epworth Sleepiness Scale; self-administered questionnaire providing a measure of a person's general level of daytime sleepiness on a scale of 0 to 24

Table 2: Consecutive therapies for the treatment of insomnia in the period prior to quetiapine use

Pharmacological therapy		
Class	**Generic name**	**Dosage (mg per day)**
Intermediate-acting benzodiazepines	Brotizolam Clotiazepam	0.25 10
Long-acting benzodiazepines	Clonazepam	0.8
Nonbenzodiazepine receptor agonists	Zolpidem	10
Antidepressants	Trazodon Mirtazapine	200 15
Noradrenalin- and serotonin reuptake inhibitors	Venlafaxin	75
H1- antihistamines	Hydroxyzine dihydrochloride	87.5
Other treatments		

Medical: Continuous Positive Airway Pressure
Psychotherapy: Cognitive Behavioural Therapy for insomnia (CBTi) Relaxation therapy