CASE REPORT

Paradoxical insomnia in a patient taking zopiclone

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SUMMARY

We present a case of a man aged 20 years who was diagnosed with a major depressive disorder and was started on escitalopram and zopiclone. The patient had a significant response to escitalopram except that he developed severe insomnia which dramatically resolved following discontinuation of zopiclone. The patient was recommenced on low dose of zopiclone and unfortunately redeveloped moderate insomnia. The patient was thoroughly investigated and zopiclone was determined to have paradoxically caused the insomnia.

BACKGROUND

Zopiclone is a commonly prescribed non-benzodiazepine hypnotic drug and it is used as a short-term treatment strategy to improve sleep in a number of psychiatric disorders. It is extremely rare for zopiclone to cause insomnia as a side effect. We present a patient who developed severe insomnia as a result of the short-term use of zopiclone.

The patient was a man aged 20 years who was diagnosed with a major depressive disorder (MDD) (DSM-V) and was started on escitalopram with beneficial effect for the predominant affective symptoms except for sleep disturbance. The patient was then started on zopiclone and consequently developed a severe insomnia which only resolved after withdrawal of zopiclone and attempt to reintroduce zopiclone at a lower dose resulted in re-emergence of insomnia.

Rebound insomnia had been previously reported following sudden withdrawal of zopiclone. However, we have not come across any case report of intractable insomnia as a direct consequence of the use of zopiclone. It is therefore important to be aware of such an extremely rare side effect when treating patients with worsening insomnia, despite adequate dosage of zopiclone.

CASE PRESENTATION

We present a man aged 20 years who presented to our psychiatric outpatient clinic with a 3-month history of symptoms of depression characterised by low mood, anhedonia, decreased motivation, lack of energy, recurrent suicidal ideas and decreased total sleep time from his baseline of 9 hours per night to 6 hours. There were no associated features of psychosis or bipolar disorder. No history of substance abuse, including alcohol, coffee and tobacco. No chronic or acute physical illness, no history of head injury and his physical examination were negative to any stigmata of neurovascular disorder. He had a stable and supportive psychosocial environment. He has a positive family history of MDD. A diagnosis of MDD was made using DSM-V

criteria.¹ The patient was started on escitalopram which was optimised to a daily dose of 20 mg every morning. The patient's symptoms significantly reduced except for increased sleep latency, despite a self-report of healthy sleep hygiene.

There was no reason to doubt his medication adherence. He was prescribed zopiclone 7.5 mg at bedtime and within 2 days, he was reporting worsening sleep quality but had no other features of mood disorder. Zopiclone was optimised to 15 mg at bedtime, but unfortunately, he developed intractable insomnia characterised by increased sleep latency, decreased total sleep time from baseline of 9 to 3–4 hours and overall dissatisfaction with quality of sleep. The patient was referred for sleep study, which ruled out primary insomnia.

INVESTIGATIONS

The following investigations were performed.

Drug urine screening was negative to illicit substances, including benzodiazepines. CBC (diff), electrolytes, thyroid function test and liver enzymes were normal. EEG shows a mild intermittent bihemispheric disturbance of cerebral activity; no frank epileptiform abnormalities were seen. CT scan of the brain was normal.

DIFFERENTIAL DIAGNOSIS

We initially thought that this may be an atypical presentation of a bipolar affective disorder. However, there was no persistent elevation of mood or lability of mood. There was no evidence of inflated self-esteem or overtalkativeness and no flight of ideas or racing thoughts. There was no family history of bipolar disorder.

Anxiety disorder was a second differential diagnosis. However, there were no evidence of phobias or free floating anxiety and no history of panic attack. There was no evidence to support post-traumatic stress disorder.

The patient had no associated medical comorbidities such as coronary heart disease, obstructive airway disease or endocrine abnormalities.

We also considered the possibility of primary insomnia but were ruled out following assessment by a sleep specialist.

OUTCOME AND FOLLOW-UP

The sleep specialist advised active treatment of the depressive disorder. Hence, optimisation of escitalopram to maximum dosage and further change of antidepressants to duloxetine and mirtazapine and a combination of the latter with escitalopram and cognitive-behavioural therapy focusing on anxiety management and psychoeducation on sleep hygiene were started. Unfortunately, the patient continued

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to have insomnia for over 6 weeks despite active treatment protocol as mentioned above. We decided to decrease zopiclone to 7.5 mg from 15 mg bedtime.

Consequently, the patient reported a moderate improvement of sleep within 24 hours of dose reduction in zopiclone. It was then decided to discontinue zopiclone which resulted in dramatic improvement of sleep back to baseline of 9 hours per night.

The patient consented to a reintroduction of zopiclone at a much lower dose of 3.75 mg at bedtime and almost within the same day, there was a modest disruption in sleep quality with return to normal sleep after stopping the zopiclone 3.75 mg at bedtime.

The patient is currently in remission of his MDD and stabilised on escitalopram 20 mg daily.

DISCUSSION

Zopiclone belongs to a new generation of hypnotic drugs along with zolpidem and zaleplon. They are generally termed as the Z-drugs. Zopiclone is a cyclopyrrolone, a class of non-benzodiazepine hypnotic. It is a α -1 isoform selective agonist of GABA-A/benzodiazepine receptors. Zopiclone involves in allosteric modulation of the GABA-A receptor, thus enhancing the inhibition of GABA and boosting chloride conductance through GABA-regulated channels. Through this action on sleep centre, zopiclone causes sedative hypnotic effects. Zopiclone does not distinguish between GABA-A receptors containing different α -subunits (BZ1 and BZ2 phenotype). Zopiclone is recommended for the short-term treatment of primary insomnia and insomnia due to psychiatric disturbances.² The product monograph reported rebound insomnia with sudden discontinuation of zopiclone but not intractable insomnia while on the medication.³ Other commonly reported side effect of zopiclone is the so-called 'hangover effect' due to delayed elimination, so there may be a prolonged drug effect resulting in residual sedation or the hangover effect.⁴ This side effect of zopiclone may be useful for sustained treatment of insomnia with less waking during the night.⁵ This is the opposite in the case of our patient. There may be a possible explanation of drug interactions between zopiclone and antidepressants as our patient was concomitantly on escitalopram and mirtazapine. Zopiclone is metabolised by different microsomal enzymes and a panel of heterologously expressed Cytochrome P-450 isozymes and CYP3A4 is the major enzyme involved in zopiclone metabolism. The CYP3A4 are inhibitors and inducers and thus have a lesser effect on their bioavailability of antidepressants,⁶ and similarly, there is no significant effect of antidepressants on zopiclone metabolism.⁷ It is not uncommon to observe paradoxical aggression with the use of benzodiazepines and therefore not entirely surprising for a

GABA modulating drug like zopiclone to rarely cause a paradoxical effect. However, unlike benzodiazepines idiosyncratic effects, a dose-related insomnia was observed in our patient while on zopiclone.

Learning points

- ▶ Insomnia can be a symptom of various psychiatric disorders and zopiclone is seen as a safe drug for treating insomnia, especially with its lower risk of dependence relative to benzodiazepines.
- ▶ It is important to be aware of the potential paradoxical insomnia caused by zopiclone while treating sleep disturbances; otherwise, patient could be exposed to unnecessary risks of polypharmacy or generous dosages of either antidepressants or antipsychotic drugs.
- ▶ Clinicians should pay particular attention to intractable insomnia in the absence of core features of a specific disorder under treatment.
- ▶ It is prudent to consider sleep specialist referral and if necessary consider dose reduction in hypnotics.

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Competing interests None declared.

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