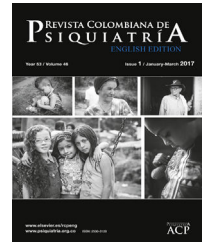




REVISTA COLOMBIANA DE PSIQUIATRÍA

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Case report

Zolpidem dependence and withdrawal. A case report of generalized seizures



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ARTICLE INFO

Article history:

Received 19 January 2021

Accepted 21 June 2021

Available online 18 October 2023

Keywords:

Zolpidem

Substance withdrawal syndrome

Seizures

ABSTRACT

Zolpidem is a non-benzodiazepine hypnotic agent used most frequently in the treatment of insomnia, indicated for short-term use. It is not indicated for the chronic treatment of sleep disorders, despite which there is evidence in clinical practice that a large number of patients receive it for years. Although it has been described that it presents a better profile of adverse effects than benzodiazepines and that it generates a lower risk of dependence and withdrawal than these, there are significant reports of cases of dependence and withdrawal from zolpidem. A report of a case of generalized tonic-clonic seizures due to withdrawal at a dose of 300 mg per day of zolpidem is presented and a brief review of the literature is carried out.

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Dependencia y abstinencia de zolpidem. Reporte de un caso de convulsiones generalizadas

RESUMEN

El zolpidem es un agente hipnótico no benzodiazepínico utilizado con suma frecuencia en el tratamiento del insomnio e indicado para emplearlo en el corto plazo. No está indicado para el tratamiento crónico de los trastornos del sueño, pese a lo cual se evidencia en la práctica clínica que gran cantidad de pacientes lo reciben por años. Si bien se ha descrito que presenta un mejor perfil de efectos adversos que las benzodiazepinas y que genera menos riesgo de

Palabras clave:

Zolpidem

Síndrome de abstinencia de

sustancias

Convulsiones

DOI of original article: <https://doi.org/10.1016/j.rcp.2021.06.007>.

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dependencia y abstinencia que estas, existen sendos reportes de casos de dependencia y abstinencia de zolpidem. Se presenta el reporte de un caso de convulsiones tónico-clónicas generalizadas por abstinencia a dosis de 300 mg/día de zolpidem y se realiza una breve revisión de la literatura.

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Introduction

Zolpidem is a non-benzodiazepine hypnotic agent which chemically belongs to the imidazopyridine family. Along with zopiclone, eszopiclone and zaleplon, it is one of the so-called Z drugs, with specific hypnotic action, mainly sleep inducers.¹ Zolpidem is one of the most used drugs in this group of hypnotics. It generates its pharmacological action via the GABA A benzodiazepine receptor and binds preferentially to receptors containing the alpha-1 subunit.² It thus facilitates induction and increases sleep time, reduces the number of awakenings and the latency period and improves sleep quality.

Zolpidem has a favourable pharmacokinetic profile for its use as a hypnotic, as it is absorbed and eliminated quickly.³ Gender-related pharmacokinetic differences have been reported, with higher zolpidem plasma concentrations in women, who have slower drug metabolism and clearance.⁴ Higher morning serum concentrations are therefore detected in women after taking it at night, which may mean a greater risk of adverse effects compared to men.⁵

Since its discovery, due to its mechanism of action, it has been described as having a lower risk of dependence or abuse compared to benzodiazepines.⁶ Although it is clinically effective for treating sleep disorders and is better tolerated than benzodiazepines, it has multiple adverse effects.⁷ The main ones are headache, falls, drowsiness, morning hangover, dry mouth and some memory disorders.¹ Cases of sleepwalking have also been reported.⁸

Zolpidem has become the most prescribed hypnotic drug in the United States in the last 25 years.⁹ Some authors highlight that it is effective for the short-term treatment of insomnia and should be prescribed for no more than 10 days. If the patient's insomnia does not resolve, other possible causes should continue to be assessed.¹

In this report, we describe a case of abuse of, dependence on and withdrawal from zolpidem and discuss the withdrawal symptoms of high doses of this drug.

Case report

This was a 35-year-old patient with a 14-year history of sleep disorders. He had been given multiple psychiatric and psychological treatments, with poor adherence. In recent months he had been having virtual therapy, due to the isolation situation resulting from the COVID-19 pandemic. He had been prescribed quetiapine 25 mg/day and sertraline 50 mg/day for his anxiety disorder, although he had not adhered to that prescription. The patient had been buying zolpidem on a website

(medicamentossinreceta.com [medicines without a prescription.com]) without a prescription, four boxes at a time, and then proceeded to stop taking them. In the last weeks before he was admitted to hospital, he had been taking up to 30 zolpidem tablets per day, equivalent to 300 mg/day. Because he had stopped taking the medication, 48 h later, he suffered an episode of psychomotor agitation, which led to his hospitalisation. During this, he had two episodes of generalised tonic-clonic seizures. A complete physical examination and other tests were performed. The result of the clinical neurological examination was normal, as was his blood count. Brain computed tomography (CT) was normal, with no evidence of acute lesions. As a relevant previous medical history, he had suffered a similar episode two years earlier in the context of withdrawal from megadoses of zolpidem, which did not require hospitalisation.

During his stay in hospital, he was medicated with levitracetam 1,500 mg/day and lorazepam 1 mg/8 h, and had no repeat of the episode. He was then referred to a specialised centre to treat his dependence on and abuse of zolpidem.

Discussion

Although zolpidem has classically been considered a safer drug than benzodiazepines, multiple cases of abuse of, dependence on and withdrawal symptoms from this drug have been reported in the literature.¹⁰ At supratherapeutic doses, zolpidem can cause abuse, dependence and, as a serious withdrawal symptom, seizures.¹ The usual recommended dose is 10 mg daily.¹⁰ Supratherapeutic doses are described as >60 mg/day.¹¹

Pichot et al.¹⁰ reported the case of a patient who started having seizures after abrupt discontinuation of a high dose of zolpidem. Hajak et al.¹² conducted a review of case reports which included 36 cases of zolpidem dependence and 22 of zopiclone dependence. In 2011 Wang et al.¹³ reported two cases of zolpidem dependence and seizures after abrupt discontinuation of a high dose (200–400 mg per night in one case and 400–500 mg per night in the other). When zolpidem was abruptly discontinued, patients suffered from anxiety, general insomnia, restlessness and tonic seizures.

Cubala et al. described the case of a 29-year-old woman who suffered generalised seizures after abruptly discontinuing zolpidem, which she was taking in doses of 160 mg/day. They emphasise that the patient was dependent.

Seizures have been reported in the context of withdrawal from zolpidem with doses ≥ 100 mg daily.

As mentioned above, zolpidem is currently one of the main drugs prescribed as a hypnotic for the treatment of insomnia.⁸

It should be highlighted that its use is not indicated nor recommended for the long-term treatment of a sleep disorder, only being indicated for short periods.

Generally, medical professionals do not tend to prescribe more than 20 mg/day, and using megadoses or supratherapeutic doses, which may later generate seizures in the case of withdrawal, is rare. In clinical practice, it is evident that patients are dependent on zolpidem and, although its indications contain a warning not to use the drug for a prolonged period, many patients tend to take it for years.

Conclusions

Zolpidem is a commonly prescribed drug not only in Psychiatry but also in various medical specialties. There are many reports of misuse or abuse, so when prescribing zolpidem, the possibility of developing dependence and subsequent withdrawal symptoms must be considered, as these are common adverse effects. Greater caution should be taken in women, because their metabolism of the drug is slow, which generates a greater risk of serious adverse events.

We need to stress the importance of reinforcing the indication when prescribing it for the first time and psychoeducating the patient on therapeutic alternatives for the treatment of insomnia, whether pharmacological or non-pharmacological.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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