Scientific Research Publishing

Case Reports in Clinical Medicine, 2023, 12, 213-217
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Somnambulism: Varenicline-Induced Sleep Driving

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How to cite this paper: Alkhuja, S., Girgis, M., Ali, M., Patel, P. and Odeyemi, O. (2023) Somnambulism: Varenicline-Induced Sleep Driving. *Case Reports in Clinical Medicine*, **12**, 213-217.
https://doi.org/10.4236/crcm.2023.127030

Received: June 23, 2023
Accepted: July 4, 2023
Published: July 7, 2023

Abstract

Background: Varenicline, which is derived from the cytisine compound, is used to assess in smoking cessation. Sleep driving (SD) is often classified as a variant of somnambulism. Although, somnambulism has been reported as a side effect of varenicline, varenicline-induced sleep driving (VISD) has not been reported. **Case Report:** A 56-year-old man with a history of 35 pack year smoking who presented for smoking cessation counseling. Treatment with varenicline was initiated. In the following night, the patient drove to a shopping center and woke up in his car. Varenicline was discontinued. SD has not been reported in the following nights. In a repeated attempt to stop smoking, treatment with varenicline was resumed by the patient. SD reoccurred in the following night. Varenicline was discontinued indefinitely, and SD has not been reported.

Keywords

Varenicline, Sleep Walking, Arousal Parasomnia

1. Introduction

Varenicline tartrate was originally developed as a smoking cessation agent based on the molecular structure of cytisine [1]. SD is often classified as a variant of somnambulism. Although, somnambulism is a side effect of varenicline [2], VISD has never been reported as a side effect of Varenicline.

2. Case Report

A 56-year-old man, with a history of 35 pack year smoking, who presented for smoking cessation. Previous attempts of smoke cessations, by using nicotine

supplements and bupropion have failed. The patient had no personal or family history of somnambulism. There was no history of alcohol or substance abuse. There were no other precipitating factors for SD, such as fever, stress, sleep deprivation, obstructive sleep apnea (OSA) or other arousal-related disorders. Physical examination was unremarkable.

Treatment with 0.5 mg of varenicline every 12 hours, was initiated. That night, the patient drove to a shopping center and woke up, hours later, in his car. The patient had no trauma or recall of the event. Varenicline was discontinued. SD was not reported in the following nights. In a repeated attempt to stop smoking, treatment with varenicline was resumed by the patient. VISD reoccurred in the following night. Varenicline was discontinued indefinitely and SD has not been experienced since. The development of SD upon exposure to varenicline twice is strongly suggestive that SD is a side effect to the use of varenicline.

3. Discussion

Varenicline acts as a selective and partial agonist of $\alpha_4 - \beta_2$ nicotinic acetylcholine receptors (nAchR) in the brain, with smaller affinity for $\alpha_3 - \beta_4$ in autonomic ganglia [1]. Varenicline attenuates nicotine-induced locomotor sensitization, blocks nicotine conditioned place preferences, reduces nicotine self-adminstration, blocks nicotin's brain stimulation, and attenuates the dysphoria associated with nicotine withdrawal [1]. Varenicline increases dopamine (DA) levels in dorsum striatum and in the nucleus accumbens (NAs) [3].

Cases of medications induced SD, were reported only with two medications, zolpidem and sodium oxybate (SO) (**Table 1**) [4]-[10]. The potential risk factors

Table 1. Medications inducing sleep driving.

Medicine	Reference	Cases	Comments
Zolpidem	Doane *et al.* [4]	1	48 year man developed SD after taking 10 mg of zolpidem, SD occured a year earlier when he took un-intentional 30 mg of zolpidem, which may be related to zolpidem-induced self-intoxication (ZISI).
Zolpidem	Schenck *et al.* [5]	2	Two cases of SD, in an abstract, no detailed clinical information.
Zolpidem	Hoque *et al.* [6]	1	51 year old woman with history of insomnia, developed SD few weeks after initiating zolpidem.
Zolpidem	Poceta *et al.* [7]	1	65 year old woman took one tablet of zolpidem then drove to a parking lot and slept in her car till morning.
Zolpidem	Paulke [8]	2	Two patients experienced SD after taking 1 tablet of zolpidem. However, toxicology analysis suggested the intake of more than one zolpidem tablet, suggesting ZISI.
Sodium oxybate	Wallace *et al.* [9]	1	42 year old man has a history of narcolepsy-cataplexy and OSA. Being treated with SO. Two weeks after reaching the dose of 8 g/night, he experienced SD. SO dose was decreased to 7 g/night and SD was resolved. When SO was increased back again to 8 g/night, SD reoccurred.
Sodium oxybate	Wang *et al.* [10]	1	A patient was receiving SO. On the night of SD the patient consumed alcohol. SO was continued without any episodes of SD without alcohol consumption.

Table 2. Potential risk factors for medications-associated sleep driving.

1. Concomitant ingestion of alcohol [7] [10], or sedating medications [7].
2. Concomitant sleep disorder such as OSA [7] [9].
3. History of parasomnia [7].
4. Hypnotic sedative ingestion at times other than habitual bedtime [7].
5. Hypnotic sedative ingestion when sleep deprived [7].
6. Poor management of pill bottles [7].
7. Dose dependent ZISI [4] [8], SO [9].
8. Living alone [7].

for zolpidem-related and SO-related SD are outlined (**Table 2**) [4] [7] [8] [9] [10].

On the contrary to what reported by Zadra *et al.* that somnambulism adulthood has harmful consequences [11], our reported case of VISD and other reported cases of zolpidem or SO related-SD [4]-[10] were not associated with any injuries. However, the Federal Aviation Administration banned varenicline use in pilots in May 2008, and accidental injury warning remains on the package insert today [1].

***SD as a result of increased GABA and/or DA levels*:**

Medications may induce somnambulism by enhancing Gamma-aminobutyric acid (GABA) activity at the $GABA_A$ receptors [12]. Varenicline, like nicotine, stimulates presynaptic GABA release [13], which may explain SD in our case. Furthermore, Mitall *et al.* suggested that varenicline increases DA levels in the NAs which results in increased motor activities [14]. Yet another possible explanation to VISD.

***SD occurs during the co-existence of sleep and wakefulness*:**

Brain imaging by single-photon emission computed tomography (SPECT) during a sleepwalking episode showed activation of frontoparietal cortex (typical of sleep), and co-activation of the posterior cingulate and anterior cerebellum (typical of wakefulness) [11]. These findings support the co-existence of sleep and wakefulness during somnambulism.

Surface electroencephalogram (EEG) [11] and deep EEG [15] studies showed that EEG patterns related to sleep and wakefulness can coexist and may obtain a sleep in different brain regions [11] [15]. Somnambulism was described as a disorder of arousal. Zadra *et al.* studied the postarousal EEG patterns [11]. The findings suggest that sleepwalkers are caught between non-rapid eye movement (NREM) sleep and full EEG arousal and are thus neither fully awake nor fully asleep during episodes [11].

4. Future Research

The genetic studies are the ones with the most solid supportive connections between genes and the development of somnambulism have been done. Heidbred-

er *et al.* found that not only sleepwalking but NREM parasomnia irrespective of the type is associated with HLA DQB1* 05 alleles [16]. Another promising study is the one that targeted the adenosine deaminase (ADA) gene, in which a single sleepwalking family, genome-wide analysis identified a locus on chromosome 20, where ADA lies [17]. Further genetics studies need to be done.

5. Conclusion

VISD is a side effect of varenicline use. The possible explanations for VISD are stimulation of pre-synaptic GABA release [13] or increased DA levels in NAs [14].

Physicians can minimize VISD by addressing or treating potential risk factors for medications-induced SD (**Table 2**). Patients should be assured that if VISD occurs, it is usually harmless and resolves with the discontinuation of varenicline.

Zolpidem related-SD, maybe dose-independent [5] [6] [7] or dependent like the cases of ZISIs [4] [8]. SO-related SD may occur with the consumption of alcohol [10], or with the presence of OSA and narcolepsy-cataplexy plus the consumption of a higher dose of SO [9].

VISD, in our patient, was associated with anterograde amnesia, on the contrary, 80% of cases reported by Zadra *et al.*, remembered sleep mentation during somnambulism episodes [11]. The anterograde amnesia can be explained by an arousal from slow-wave sleep into wakefulness, then returning to sleep after SD.

SD should be distinguished from impaired driving due to misuse or abuse of sedative/hypnotic drugs [18], in which drivers are often severely physically impaired resulting in driving under influence [18]. While in SD, drivers were not physically impaired and ended their driving safely at a destination.

Somnambulism is not a known symptom of nicotine withdrawal [19]. If VISD occurs, the patient still should be encouraged to pursue smoke cessation, with alternative modalities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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