Doxylamine Addiction: A Case Report

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SUMMARY
Doxylamine succinate, one of the antihistamines available without a prescription for patients suffering from insomnia, is also an antihistamine with the potential for abuse. Although there are case reports about the addictive potential of antihistamines, there are not many studies on doxylamine succinate addiction in the literature. To our knowledge, there have been no case reports on doxylamine succinate addiction in Turkey. This case report presents a patient (43, M), who started using over-the-counter doxylamine succinate at 25 mg/day due to insomnia, gradually increased to 125 mg/day for the last 3 years continuing his doxylamine succinate intake for 5 years uninterrupted, as well as his treatment process. In addition, possible causes and consequences of doxylamine succinate and the potential for abuse of antihistaminic drugs are discussed through the case.

Keywords: Antihistamines, drug dependence, doxylamine

INTRODUCTION
Doxylamine succinate (DS) is a first-generation H1 antagonist with nonspecific anticholinergic and sedative effect, available over-the-counter (OTC) and approved by the FDA in 1978 for the treatment of sleep disorders in adults. Due to its relatively long half-life (10-15 hours) and moderate sedative effect, it may lead to morning drowsiness. Over time, tolerance to sedative effects may develop. Also with an anticholinergic activity, it may cause confusion, blurred vision, and urinary retention. Its use for longer than two weeks is not recommended (Yetkin 2016).

The OTC availability of DS provides patients with the convenience of managing minor ailments without seeing a doctor, as is the case with most over-the-counter drugs. Patients may misuse or abuse antihistamines such as DS and dimenhydrinate (DH), in view that a drug not requiring a doctor’s prescription may be more innocent or harmless (Coombes and Cooper 2019). They may also develop physical or psychological dependence due to overuse. It is thought that antihistamines may be abused and addicted-to by activating dopamine neurotransmission in the nucleus accumbens through H1 receptor antagonism (Bahji et al. 2021). Cases of antihistamine addiction such as DH and diphenhydramine have been described in literature (Thomas et al. 2009, Gracious et al. 2010, Schifano et al. 2021). Although there are not many studies on the prevalence of doxylamine addiction, in a study on over-the-counter drugs in pharmacies, it was found that 72.2% of the 36 people using DS continued it for more than 1 month and 61.5% more than 6 months. Additionally, one of them met the DSM-IV addiction criteria and had been using DS for 4 years (Roussin et al. 2013). Pheniramine and dimenhydrinate addiction cases related to antihistamines have been previously reported in Turkey (Bilici et al. 2012, Kaya 2014). To the best of our knowledge, this is the first case of doxylamine succinate addiction reported in Turkey. In this article, a patient who has been using DS continuously for 5 years is presented.

CASE
A 43-year-old, male patient married with two children, who worked as a teacher, applied to our outpatient clinic with the complaint of difficulty in falling asleep for two or three months despite using DS continuously every day for 5 years, with a dosage of 125 mg/day for the last 3 years. He kept on using the medication because when he stopped, he reportedly had symptoms of restlessness, nausea, sweating, headache, and insomnia. Sedative, Hypnotic, and Anxiolytic-Related
Disorder according to DSM-5 (F13.20 Sedative, Hypnotic or Anxiolytic Dependence according to ICD-10) were considered in the initial diagnosis of the patient, as he met the criteria of drug addiction such as keeping at least 10 boxes of DS at home, using doses larger than the recommended dose (25-50 mg/day), always keeping the drug available on himself wherever he was going, not being able to quit the efforts, despite his complaints. After four weeks, his depressive complaints decreased partially (HAM-D: 14), he took 50 mg/day for the first two weeks and 25 mg/day DS for 3-4 days a week for the last two weeks without experiencing severe restlessness and insomnia. Diazepam 15 mg/day was added to his drug regimen. It was noted that his depressive complaints were gone (HAM-D: 7) and he did not report experiencing any DS-withdrawal symptoms except one day he took 25 mg of DS following an argument with his wife. Diazepam was gradually discontinued within one week and treatment with venlafaxine 75 mg and mirtazapine 15 mg was continued. The patient reported that he had taken DS 25 mg/day, a total of 5 times, from the 2nd to the end of the 5th month of his treatment, usually following a stressful event and that he had no desire to take DS and did not take any DS for the last month. Monthly follow-up of the patient, whose mood was euthymic and whose depressive complaints have resolved completely, continues.

DISCUSSION

Insomnia is defined as having difficulty falling asleep and insufficient duration, integrity, and quality of sleep despite sufficient time or opportunity. Insomnia is a very common complaint. While 30-50% of the population have short-term insomnia, 10-15% have chronic insomnia (Yetkin 2016). Approximately 25% of people with sleep disorders use OTC sleep aid medications. Although use of DH and DS, which are commonly used as OTC sleep aids, is not recommended for more than 2 weeks, many adults use these drugs chronically (Krystal et al. 2019). In a study investigating such chronic use, 21% of people aged 18-64, 37% of people aged 65-74, and 47% of people over 75 reported having used an over-the-counter sleep aid for more than 15 days in the previous month. Considering the possibility of concomitant anticholinergic drug use by older adults and the frequency of alcohol use by young adults, it has been suggested that great attention should be given to the possible side effects in chronic use of antihistamines (Albert et al. 2017).

In laboratory tests, antihistamines have been reported to act as antidepressants or to have anxiolytic effects in psychiatric patients. It is believed that the pharmaceutical effect of these drugs will not be limited to the histamine system alone. There is evidence that antihistamines may interact with acetylcholine, serotonin, norepinephrine, dopamine, and the opioid system. This may explain their effects on depression and anxiety (Roussin et al. 2013). In this presented case, the patient's need to take DS to reduce his anxiety in stressful situations such as arguing with his spouse may be related to the anxiolytic effect of DS. The decrease in the frequency of DS use in parallel with the decrease in depressive complaints may support the view that antihistamines have an antidepressant effect.
The potential for abuse of antihistamines may be related to their interaction with the dopamine system, which plays a role in the enhancing effects of many substances (Esposito et al. 2020). The enhancing effects of amphetamine and cocaine are critically dependent on the release of dopamine in the nucleus accumbens. Neurochemical evidence, such as H1 antagonism causing an increase in dopamine levels in the nucleus accumbens and preventing dopamine reuptake in the striatum, supports this opinion (Esposito et al. 2020, Bahji et al. 2021).

Psychiatric complaints are often prominent in individuals who abuse antihistamines. Most of the reported cases include patients diagnosed with schizophrenia, depression, anxiety disorder, or substance abuse (Esposito et al. 2020). Patients followed-up in psychiatry outpatient clinics may not inform doctors about their use of over-the-counter drugs, which they believe are harmless. In this presented case, although insomnia is the underlying reason for going to the outpatient clinic, it is quite remarkable that depressive complaints and DS addiction were also part of patients’ medical history, and that DS addiction has also been treated together with depressive disorder with antidepressant and anxiolytic treatment applied in combination with gradual DS dose reduction. Antihistamines with anticholinergic and sedative effects can be added to the treatment in order to reduce the extrapyramidal side effects of antipsychotics in schizophrenia patients, which is yet another patient group frequently followed-up in psychiatry outpatient clinics. However, it has been stated that during chronic use, patients with schizophrenia may also have a tendency to abuse antihistamines, and high-dose antihistamine intake may aggravate psychotic complaints (White et al. 2015). Questioning and addressing the use of over-the-counter drugs in patients followed-up in the psychiatry outpatient clinics is one of the first steps towards the reduction of drug abuse.

It has been stated that gradual dose reduction in the treatment of cases with reported antihistamine dependence is the only detoxification treatment plan that has been shown to alleviate withdrawal symptoms (Thomas et al. 2009). In a patient with DH addiction and depressive disorder, escitalopram 10 mg/day and mirtazapine 15 mg/day were started, in addition to gradual dose reduction and recovery was achieved (Kaya 2014). In a 15-year-old patient with bipolar disorder type 2 and anxiety disorder with a history of an opioid use disorder, oral naltrexone was started gradually (50 mg/day) for hydroxyzine addiction which was started to relieve his anxiety, and withdrawal symptoms were reported to have resolved (Gracious et al. 2010). DS and other antihistamines, which are sold without a prescription and the use of which cannot be controlled have the potential for abuse/dependence as well as the burden of side effects caused by chronic use (Thomas et al. 2009, Roussin et al. 2013). Other important aspects are that people who have developed addiction cannot be detected and evaluated in terms of accompanying psychiatric disorders. This case is particularly noteworthy both due to uninterrupted use of DS well above the recommended dose of 125 mg/day for 5 years, and also because of the cessation of abuse in parallel with the treatment of a comorbid depressive disorder. The awareness and attention of psychiatrists, family physicians, and pharmacists of the abuse/addictive potential of DS and other antihistamines, and informing the patients about the abuse potential and the side effects will help prevent such abuse.

REFERENCES


