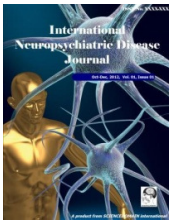

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Antihistamine Drug Misuse and Dependency in Headache Patients: A Case Series in a Tertiary Care Headache Center

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Authors' contributions

This work was carried out in collaboration between all authors. Author MJM designed the study. Author ZE managed the literature searches, reviewed patient charts, collected data and wrote the first draft of the manuscript. Author MJM managed the analyses of the study and wrote final manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To report antihistamine abuse at a tertiary headache center including 6 patients who meet the criteria for substance abuse for intramuscular diphenhydramine (DPH).
Presentation of the Cases: Six patients were identified who were prescribed intramuscular DPH and developed escalating drug use. All patients were female, with a mean age of 40.6 (32-53), with diagnosis of medication overuse headache. Five had chronic migraine and 1 new daily persistent headache. All 6 patients were disabled. Three patients had history of misuse of other drugs including benztropine, hydromorphone and clonazepam. Comorbid psychiatric disorders included 3 patients with major depressive disorder, 2 with ADHD, 1 with post-traumatic stress disorder and social phobia. All of these patients had a history of receiving intravenous DPH as part of their migraine treatment to avoid complications from neuroleptics.
Discussion and Conclusion: A literature search revealed eight case reports of DPH abuse

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including a total of nine patients, published between 1986 and 2014. Medical charts were reviewed at Jefferson Headache centre and identified 6 patients with intramuscular DHP abuse. Clinicians treating migraine should be aware of potential risk for DPH abuse. Intramuscular and intravenous forms of the drug should be limited to inpatient use, if possible, and should be avoided in patients with history of drug abuse and medication overuse.

Keywords: Diphenhydramine dependence; intramuscular injection; headache.

1. INTRODUCTION

Antihistamines have a role in acute migraine treatment in treating or preventing akathisia and dystonia from neuroleptic use and many migraine prophylactic medications (tricyclic compounds, flunarazine, cyproheptadine) have antihistamine effects.

The potential for antihistamine drug addiction and misuse has been well documented and appears to be associated with the ability of these compounds to elevate mood, increase energy levels and, produce hallucinogenic effects [1]. Increases in dopaminergic neurotransmission in mesolimbic brain pathways following antimuscarinic administration may produce rewarding properties and drug-seeking behavior. They also have the potential to increase the effect of co-administered drugs such as opioids. The neuronal pathways of drug addiction are components of the mesocorticolimbic dopamine systems that originate in neurons in the ventral tegmental area. Both natural rewards (food, drink, and sex) and addictive drugs stimulate the release of dopamine from neurons of the presynaptic ventral tegmental area into the nucleus accumbens, causing euphoria and reinforcement of the behavior. In the case of natural rewards, there is a very rapid adaptive change, or habituation, after a few experiences [2].

Substance abuse, in the DSM-IV is defined as the recurrent use of a substance despite persistent severe adverse events, often leading to a failure to meet personal responsibilities. This would include social, legal and intrapersonal problems which are exacerbated by the substance abuse, and use in situations which are hazardous such as driving a car. Substance use disorder in DSM-5 combines the DSM-IV categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe [3].

The sedative action of DPH was thought to limit its potential for abuse. However, Pates et al. [4] found that almost half of the pharmacists questioned in a survey suspected that DPH was subject to misuse. This constituted the second most commonly cited product behind a Kaolin and Morphine mixture. Similar surveys of pharmacists' perceptions also found antihistamine-containing sedatives to be the second most misused group [5]. Published evidence suggests that doses of DPH between 300–700 mg are associated with hallucinogenic effects and are used recreationally [6]. Multiple case series and case reports document the experience of antihistamine abuse in adolescents [7] and adults [8] resulting in delirium, ataxia or psychosis. The majority of case reports describe men in their thirties with history of schizophrenia being treated with first generation antipsychotics. The documented reasons for misuse included insomnia, calming effects and mild euphoria. The daily doses of DPH used, ranged from 480–3000 mg, compared with the usual therapeutic dose for insomnia of 50 mg [9].

A literature search revealed eight case reports of diphenhydramine abuse including a total of nine patients, published between 1986 and 2014 [10,11]. We report our experience with antihistamine abuse at a tertiary headache center including 6 patients who meet the criteria for substance abuse for intramuscular diphenhydramine.

2. MATERIALS AND METHODS

Electronic medical records (EMR) of patients having antihistamine medications has been reviewedin their active medication list and an office visit since 2012 at our tertiary outpatient center. We obtained approval from the Thomas Jefferson University Institutional Review Board for this study. The authors reviewed these medical charts including prescriptions, interviewed physicians or nurses at Jefferson Headache Center who were involved in their care, and focused on behaviors raising concern for addition or dependence. This was not a comprehensive pharmacy database study and is certainly possible that other cases, especially those patients abusing non-prescription medications, were missed.

For each patient we noted the frequency of use, and prescriptions for intramuscular medications. Escalating use, compulsive daily use, asking for intramuscular forms of the drug, using multiple providers, continued use despite severe adverse events such as weight gain or sedation, and increased phone calls such as those for early refills were considered as evidence of abuse or addictive behaviors. For each subject, risk factors and demographic profile for abuse such as age, gender, family history of addiction, history of opioid use or abuse, headache type, and medication overuse headache were considered including comorbid psychiatric disorders.

3. RESULTS AND DISCUSSION

This study identified 6 patients who were prescribed intramuscular DPH and developed escalating drug use after initiating with instructions to use DPH sparingly as a rescue for severe attacks or medication side effects. All patients were female, with a mean age of 40.6 (32-53), with diagnosis of medication overuse headache. Five had chronic migraine and 1 new daily persistent headache.All patients were not currently employed and disabled from work due to headache. Level of disability was evaluated by using MIDAS tool (Migraine Disability Assessment Questionnaire). MIDAS Score were over 21 (Grade IV-Severe disability) in all cases. Five of the six patients were college graduates. Patients were reported on their escalating and persistent requests on DPH IM injection prescriptions and refills. Despite the limitation on their prescriptions as once a week injections with one month supply and 3 refills, all patients requested additional refills before then. Numbers of documented phone calls shows the frequency of requests in (Table 1). The vast majority of these phone calls were for early refills. Most of these patients used 3 months supply in a month or 2 weeks. Although average daily doses ranged from 50-200 mg, some patients admitted to using as much as 1000 mg per use. Their daily doses remained unknown due to denial of escalating use, prescriptions from multiple providers, frequent ER visits and usage of OTC" forms of DPH. Two patients were found to have received intramuscular prescriptions for DPH from other health care providers without our knowledge. Three patients had history of misuse of other drugs including benztropine, hydromorphone and clonazepam. Comorbid psychiatric disorders included 3 patients with major depressive disorder, 2 with ADHD, 1 with post-traumatic stress disorder and social phobia. Five patients had a documented family history. 1 patient was adopted, and biological family history was unknown. 2 others had a family history of substance abuse. Table 1 all of these patients had a history of receiving intravenous DPH as part of their migraine treatment to avoid complications from neuroleptics.

4. CONCLUSION

A significant minority of patients with frequent headaches abuse intramuscular DPH and demonstrate addictive behaviors. These patients developed DPH addiction after their intravenous treatment in the hospital and subsequent outpatient usage. In the case reports we reviewed, some patients used DPH on a daily basis but others tended to take excessive doses over short periods of time to achieve the desired effects. Clinicians should be aware of potential risk for DPH abuse for patients who were under migraine treatments. History of psychiatric comorbidities and substance abuse can be used as red flags.

Table 1. Addictive behavior and escalating use of DPH in headache patients

Patient	Age	Gender	Diagnoses	Med overuse	IM or PO	Escalating use	Multiple providers	Phone calls/month
1	32	Female	CM	Yes	IM	Yes	Yes	0.9
2	34	Female	CM	Yes	IM	Yes	Yes	1.0
3	53	Female	CM, after cerebral aneurysm repair	Yes	IM	No	No	1.5
4	48	Female	CM, Post-traumatic	Yes	IM	Yes	Unknown	1.3
5	42	Female	CM	Yes	IM	Yes	Unknown	0.8
6	35	Female	CM	Yes	IM	Yes	Yes	1.5

Intramuscular and intravenous forms of the drug should be limited to inpatient use, if possible, and should be avoided in patients with history of drug abuse and medication overuse.

Most of cases of diphenhydramine abuse including a total of nine patients, published between 1986 and 2014 [10,11] had a history of major psychiatric comorbitidies. In previous studies all reported cases exhibited features of DSM-IV criteria for substance dependence, including tolerance, increasing usage, continuing use despite adverse effects (dry mouth and blurred vision), drug seeking behavior and withdrawal reactions. Five had a history of schizophrenia and were being treated with antipsychotics. One of them had history of dysthymia, panic disorder, alcohol dependence and cannobinoid abuse, and one patient had history of drug induced psychosis and multiple substance dependence.

We have begun to use oral DPH as a pretreatment with neuroleptics, reserving intravenous use for those with dystonic reactions or severe akathisia.

CONSENT

Individual patient consents are not applicable for this study.

ETHICAL APPROVAL

We obtained approval from the Thomas Jefferson University Institutional Review Board for this study.

COMPETING INTERESTS

Dr. Marmura has received honoraria from Zogenix. Dr. Ergonul has nothing to disclose.

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