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Author

Parker, Stephen, De Gioannis, Angelo, Page, Colin

Published

2013

Journal Title

Journal of Substance Use

DOI

[10.3109/14659891.2012.707285](https://doi.org/10.3109/14659891.2012.707285)

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Chronic promethamine misuse and the possibility of dependence: A brief review of antihistamine abuse and dependence, and a case report.

S. Parker & A. De Gioannis

DRAFT

Abstract

Promethazine, a phenothiazine derivative antihistamine, has not been considered to be associated with problems with dependency. A unique case, with features fulfilling the criteria of drug dependence following several years of misuse of high dose promethazine is presented. Literature relating to the abuse of promethazine and other centrally acting antihistamines, the possibility of the development of dependency with habitual use of these agents, as well as approaches to management of withdrawal, are reviewed. The need for vigilance about the potential for abuse of promethazine and other over-the counter agents by medical staff and pharmacists is emphasised.

(Abstract = 97 words)

Chronic promethamine misuse and the possibility of dependence: A brief review of antihistamine abuse and dependence, and a case report.

Background

The Product Disclosure Information and Consumer Medication Information documents for the proprietary and generic preparations of Promethazine in Australia make no reference to potential for abuse or dependence. However, there are multiple case reports detailing abuse potential of centrally acting antihistamines, with short-term recreational use predominantly in adolescents seeking euphorogenic or hallucinatory effects^{1,2} and more habitual patterns of abuse usually reported in adult females^{2,3} and in opiate dependant populations for the purposes of potentiation of opiate effects and substitution in times limited availability.^{4,5} Furthermore, there are multiple case reports documenting the potential for physiological and psychological dependency to develop in users of centrally acting antihistamines,^{2,6,7,8} but not with promethazine or the other phenothiazine derivatives. Information about patterns of abuse and misuse of anti-histamines is difficult to ascertain given that they are generally available without prescription and there is limited capacity for monitoring.²

The earliest cases identified in the literature of withdrawal features and problems with weaning in patients using antihistamines were reported in this journal in 1948.⁹ Many patients, including children,¹⁰ with abuse and dependence problems commenced without premeditation to misuse, but found their pattern of use becoming increasingly problematic overtime.¹¹ Habitual antihistamine users have described the experience of tremulousness, agitation, dysphoria⁷, irritability and muscle aches⁸ when the preferred drug is unavailable. Common features of the antihistamine discontinuation syndrome following chronic high dose self-administration during inpatient detoxification include unrest, uneasiness, depression, tremulousness and

sweating^{6,8} and increased defecation⁸ over a timeframe of days to weeks. There has been disagreement as to the extent to which these withdrawal features reflect release from the CNS depressant effects or cholinergic rebound.⁸ Multiple approaches have been taken to managing these withdrawal symptoms including split dosing with rapid or gradual weaning in inpatient settings^{7,12}, and symptomatic management with naltrexone² and antidepressants.⁵

We present the case of a patient who developed a problematic pattern of use with promethazine with features suggestive of both physical and psychological dependence. No other similar cases were identified by the authors in a review of the literature. Promethazine is a long-acting antihistamine and has multiple mechanisms of action, acting primarily as a H1 receptor antagonist but also having direct antagonist action at both muscarinic (M1) and dopamine (D2) receptors.¹³ It has been abused recreationally and in intentional overdose.¹³ It is interesting that in a sample of injecting drug users in Vietnam, 75% had used promethazine recreationally most disliked its effects.⁴ The effects in acute overdose were recently reviewed in a retrospective case series by Page et al¹³, who viewed these as being mediated by CNS depression and anticholinergic effects. The most common effect in acute overdose (median ingestion 625mg, IQR 350-1250mg) was mild-to-moderate sinus tachycardia, the most clinically significant effects being dose related delirium (42%) and mild-to-moderate CNS depression (GCS <15 in 56%). The case presented involved chronic high level overdose over a several year time period.

Case Study

A 30-year old female, who lives alone and works part-time as an allied health professional, was seen at a psychotherapy clinic. She had past history of a severe and recurrent Major Depressive Disorder that has necessitated inpatient psychiatric care

on two occasions. She indicated that promethazine was first used at the age of 23, during the sub-acute phase of recovery from an acute depressive episode, at the suggestion of a friend to assist with insomnia. She described rapid tolerance to its sedative effects with increasing doses required to achieve sleep, she later began to use it to manage anxious rumination and critical self-talk. Her pattern of abuse escalated and at the time of assessment she was taking around 15x25mg tablets in the evenings on workdays and 30x25mg tablets throughout the day on non-work days. The medication was obtained from multiple community pharmacies each week to avoid suspicion.

In conjunction with her escalating promethazine use her levels of anxiety and dysphoria worsened considerably, and she also described blurring of vision, impaired memory and concentration. Her low mood and anxiety had been poorly responsive to multiple antidepressant agents over this time. Though she minimised its significance, she acknowledged her promethazine use as problematic, and had made multiple attempts to cut down. There was no history of significant abuse of alcohol or illicit substances; however it appears that she had also tended to misuse benzodiazepines and atypical antipsychotics that had been previously trialled to assist with reducing her abuse of promethazine.

Multiple features suggestive of psychological and physiological dependency to promethazine were present. Increased amounts of the drug had been taken over time to achieve the desired effect of emotional numbing and sedation. Withdrawal features included anxiety, tremulousness, restlessness, dysphoria and craving for promethazine on waking and throughout the days when not using; these symptoms being rapidly relieved by promethazine use. She had multiple unsuccessful attempts to reduce her use of the substance, and her non-work time was predominantly centred

around intoxication and recovery from its effects. She continued to use despite adverse physical effects and repeated warnings about the dangers associated with overdose.

No abnormalities had been detected on physical review including neurological examination and review of FBC and ELFT, apart from mild bilateral mydriasis. The decision to trial a gradual weaning in the community was negotiated following discussion with the hospital alcohol and drug service and Poisons Information. After initial success with the split dose weaning she relapsed, and then elected to abruptly discontinue promethazine. She reported relatively mild withdrawal features that had largely resolved within 48 hours. The frequency of her promethazine use, and also her anxiety, dysphoria and hopelessness, have reduced markedly and she has been able to increase her work commitments. She continues to engage motivational and skills based psychological work.

Discussion

This case is significant in that it documents the possibility of the emergence of dependence to promethazine, which in this patient complicated the management of her mood and anxiety conditions, and contributed to high levels of functional impairment. Given that promethazine is widely available in Australia the case illustrates the need for caution with regards to the use of this and other centrally acting antihistamines, and for vigilance around patients' use of over-the-counter medications. The possible need for increased control around the availability of anti-histaminergic agents has been repeatedly suggested in the literature.^{6,7}

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