Case Report

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Diphenhydramine abuse and detoxification: a brief review and case report

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Abstract

Many medicines available over the counter from pharmacies are known to have abuse potential, including diphenhydramine (DPH), an antihistamine with antimuscarinic properties used for the treatment of insomnia. We present a brief review of the literature describing DPH abuse, and report the case of GF, a 56 year old woman who was admitted to an inpatient addictions unit for detoxification from DPH. A literature search revealed five case reports of DPH abuse including a total of six patients, published between 1986 and 2001. All reported cases exhibited features of DSM-IV criteria for substance dependence, and there was an apparent link with antipsychotic usage. GF was treated with antipsychotics, and was using up to thirty 50 mg DPH tablets each day. She described feeling 'good and calm' and 'it stopped the tremors'. GF tolerated a gradual dose reduction schedule, and completed the detoxification programme relatively comfortably. She was discharged from the inpatient detoxification unit as planned, and had not relapsed at six months. The described case report highlights the importance of enquiring about non prescribed medication when taking a drug history. Similarly community pharmacists or GPs should be vigilant to excessive requests for DPH, particularly in patients with a psychotic illness.

Keywords
diphenhydramine, drug detoxification, drug abuse

Introduction

Many medicines that are available over the counter from pharmacies are known to have abuse potential. Indeed, the phenomenon of over-the-counter painkiller misuse was recently highlighted in a letter to the British Medical Journal (Ford and Good, 2007). Diphenhydramine (DPH) is an antihistamine with antimuscarinic properties and is available to buy over the counter from pharmacies in the UK for the short-term treatment of insomnia. The therapeutic effect of DPH is mediated via antagonism of the histamine H_1 receptor leading to sedation. However, it also has antagonist properties at the five muscarinic cholinergic receptors (Bolden *et al.*, 1992). We present a brief review of the literature describing DPH abuse and report the case of GF, a 56-year-old woman who was admitted to an inpatient addictions unit for detoxification from DPH. A MEDLINE, EMBASE and PSYCHINFO search from 1966 to the present using the terms DPH, antihistamines, misuse, detoxification, dependence and anticholinergic was conducted to determine reasons for DPH abuse, reported withdrawal symptoms and evidence of any practical guidance on management of DPH detoxification. The papers obtained from this search were further scrutinized for relevant references.

DPH abuse

The potential for anticholinergic drug misuse has been well documented and appears to be associated with the ability of these compounds to elevate mood, increase energy levels and, in some cases, produce hallucinogenic effects (Dilsalver, 1988). Increases in dopaminergic neurotransmission in mesolimbic brain pathways following antimuscarinic administration may produce rewarding properties and drug-seeking behaviour. In patients treated with antipsychotic medication, anticholinergics may produce rewarding effects associated with a reversal of secondary negative symptoms (induced by antipsychotic treatment), and as a result, anticholinergic misuse may be particularly prevalent in patients suffering from schizophrenia (Dose and Tempel, 2000). The compound most closely linked with misuse is trihexyphenidyl, whilst the

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sedative antihistaminic action of DPH was thought to limit its potential for misuse (Dilsalver, 1988). However, when Pates *et al.* (2002) attempted to quantify the extent of abuse of over-the-counter medications, they found that almost half of the pharmacists questioned suspected that DPH was subject to misuse. This constituted the second most commonly cited product behind Kaolin and Morphine. More recently, a similar survey of pharmacists' perceptions conducted in the same geographical region also found antihistamine-containing sedatives to be the second most misused group. Of the 101 pharmacists responding to the survey, 69% felt that sedating antihistamines were subject to misuse, and 80% felt opioid products were misused (Hodson *et al.*, 2007).

The earliest report of DPH misuse came from an anonymous letter in the British Medical Journal (Anonymous, 1979), which reported that some groups of psychotropic drugs can have '… problems of dependence and compulsive use without meeting the strict definition for addiction … diphenhydramine should be included in this group'. Subsequently, Wolf *et al.* (1989) conducted a study to determine the abuse potential of DPH. Although the study included only 10 patients, was non-randomized and only conducted over a short period (less than five weeks), it is the only prospective study to address the issue and concluded that DPH had some potential for abuse. This conclusion is supported by a number of case reports, including that of de Nesnera (1996), who described two patients fulfilling DSM-IV criteria for substance misuse. Published evidence suggests that doses of DPH between 300–700 mg are associated with hallucinogenic effects and are used recreationally (Radovanovic *et al.*, 2000). Furthermore, the misuse of a gel-filled capsule formulation of DPH (Sleepia) among an unspecified number of patients prescribed methadone has also been documented (Roberts *et al.*, 1999). It caused relatively widespread concern among community pharmacists who noticed an increase in demand for the product. The gel preparation was apparently being injected by street drug users as a replacement 'downer' for the discontinued gel-filled temazepam capsules (Gelthix).

Reported cases and treatment strategies

The literature search revealed five case reports of DPH abuse including a total of six patients, published between 1986 and 2001 (see Table 1 for summary). 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 behaviour and withdrawal reactions. All six of the patients described were male, and the majority were in their thirties, had a history of schizophrenia and were being treated with first generation (typical) antipsychotics. The documented reasons for misuse included insomnia (Barsoum *et al.*, 2000), calming effects (Cox *et al.*, 2001) and mild euphoria (Feldman and Behar, 1986). The daily doses of DPH used ranged from 480–3000 mg, compared with the usual therapeutic dose for insomnia of 50 mg nocte. This is somewhat greater than the range at which hallucinations have been described by recreational DPH users. However, it must be noted that these figures represent the average daily usage, and the majority of the cases did not report the magnitude of individual doses. Interestingly, where DPH was used for its mildly euphoric properties, 1600 mg daily was reported to be divided into two 800 mg doses (Feldman and Behar, 1986), which would be expected to induce hallucinogenic effects.

In the earliest published case described by Feldman and Behar (1986), the patient had a history of schizophrenia and had been taking 1600 mg DPH daily for a month. The client was detoxified over nine days, although, unfortunately, details of the regimen used were not clear from the paper. The two patients described by de Nesnera (1996) had been using 3000 mg and 1000 mg DPH daily over a period of four months and one year, respectively. They were suffering from schizophrenia and were admitted to hospital due to medication non-compliance and worsening mental state. On admission, they were not initially prescribed DPH, although the first patient was subsequently placed on a tapering regime. In all of these cases involving rapid dose reduction (either due to immediate withdrawal or the nine-day tapering regime), severe withdrawal symptoms were experienced by patients. Some of the symptoms were similar to those seen in opiate withdrawal and included initial worsening of insomnia, irritability, restlessness, abdominal cramps, sweating and diarrhoea (Feldman and Behar, 1986; de Nesnerna, 1996). None of the reported cases described a previous history of opioid misuse, although alcohol and cannabis were used by one of the subjects.

MacRury *et al.* (1987) reported a case of a 69-year-old man with dependence to a cough medicine containing DPH. He had been consuming various quantities over a period of years and, after the death of his partner, his consumption escalated to 700 mg of DPH daily. Soon after this, he was admitted to hospital having

Table 1 Summary of case reports of DPH abuse

Case report	Patient(s) (age, gender)	Approximate daily DPH dose (mg)	Diagnosis of schizophrenia	Prescribed antipsychotic
Feldman *et al.* (1986)	34, male	1600	Yes	Thiothixene
MacRury *et al.* (1987)	69, male	700	Unknown	Unknown
de Nesera (1996)	32, male	1250–2500	Yes	Fluphenazine
	38, male	1000–1250	Yes	Fluphenazine
Barsoum *et al.* (2000)	33, male	Up to 3000	Yes	Fluspirilene and olanzapine
Cox *et al.* (2001)	34, male	480–720	Unknown	Chlorpromazine

developed fatal metabolic acidosis and hyperglycaemia, thought to be due to other ingredients in the cough medicine. The case report describes his treatment for acidosis, rather than a DPH detoxification. Similarly, Barsoum *et al.* (2000) did not document a treatment regime, but described a patient suffering from schizophrenia using 3000 mg DPH daily. He had been taking a non-prescription preparation containing DPH for six months and was co-prescribed a combination of two antipsychotic agents. The most recent case report describes a patient who had been using up to 720 mg DPH per day over a period of five months. He was co-prescribed chlorpromazine, lofepramine and diazepam, although specific details of his psychiatric history were not recorded. Treatment involved substituting chlorpromazine and lofepramine with DPH and a subsequent dose reduction over 18 weeks. There were no reported withdrawal symptoms or relapse (Cox *et al.*, 2001). Based on these somewhat limited findings, a gradual dose reduction would appear to be the best treatment strategy, with the potential to cause significantly less distress for the patient.

Summary

Despite the abuse potential of DPH, and the apparent prevalence of its over-the-counter misuse, there are relatively few reported cases of detoxification from this compound. The published cases suggest a tentative link with antipsychotic co-prescription, although the perceived scale of misuse would indicate that many cases do not reach the attention of specialist addiction services. The reviewed case reports highlight several factors to consider when devising a treatment regime and describe some of the withdrawal effects that might be expected during detoxification.

Case report

We report the case of GF (initials changed to protect client anonymity), a 56-year-old woman who was admitted to an inpatient detoxification unit for detoxification from DPH. Her past psychiatric history included a 20-year diagnosis of schizophrenia with episodes of depression. On admission, her prescribed medication was lorazepam 2 mg and temazepam 40 mg daily for insomnia, venlafaxine XL 225 mg daily for depression, olanzapine 10 mg daily and flupentixol 150 mg IM depot weekly for schizophrenia. The antipsychotic regimen had remained unchanged since her last relapse and admission two years previously. She had since been attending outpatient appointments with a psychiatrist during which time her mental state remained stable. She was also receiving medication for physical complaints, which had been stable for some time and were not considered complicating factors for the DPH detoxification.

GF started using DPH 50 mg at night to help with sleeping difficulties approximately five years earlier. Her usage gradually increased over the ensuing years until she was taking thirty 50 mg tablets each day. When asked why she started using more she replied 'The more I took, the better I felt'. She described feeling 'good and calm' and 'it stopped the tremors'. The pattern of usage at this time was structured with four to six tablets being taken every 3 hours and she would 'watch the clock' in order to take the next dose. Withdrawal symptoms appeared within hours of missed doses and included irritability, anxiety, a worsening in her tremor and muscular aching. She also complained that as her usage increased, the initial hypnotic effect had given way to insomnia ('a buzz'), and she would often remain awake for two days before becoming exhausted. She had insight into her problem but had only recently revealed the scale of her DPH usage to her community psychiatric nurse. Her main concern was severe memory impairment that had led to numerous incidents including accidental over dosages of up to 50 DPH 50 mg tablets (leading to blackouts and seizures) and frequently forgetting about food in the oven, leading to fires. The excessive quantity of tablets being bought led to her being banned from numerous community pharmacies, and she would run out of money, sell household appliances and travel up to 30 miles to a pharmacy in order to obtain further supplies.

Treatment plan

It was felt that an inpatient admission would be most appropriate for GF and have the greatest chance of achieving detoxification with minimal adverse effects. This decision was based upon GF's lack of social support in the community and the limited published information regarding DPH withdrawal, upon which a treatment strategy could be based. In light of the success of the gradual reducing regimen described by Cox *et al.* (2001), the decision was made to gradually withdraw DPH with the aim of complete abstinence. At the time of admission, GF had reduced her usage to around 400 mg per day. As a result, the inpatient-dosing schedule was initiated at 75 mg qds for three days, with gradual (25–75 mg) decrements in total daily dose every three days over a 21-day period. Given the lack of a validated withdrawal symptom scale, one was devised in order to monitor progress and adjust the rate of dose reduction, if necessary. This scale was composed of relevant components of the alcohol and opiate withdrawal scales (Sullivan *et al.*, 1989; Wesson and Ling, 2003) and focused on the previously reported withdrawal effects. Components were scored four times daily (immediately before the next dose was due) and a score of 1–7 assigned to each in order to rate severity. Symptoms assessed were blood pressure and pulse, sweating, restlessness, runny nose, lacrimation, diarrhoea, tremor, anxiety and insomnia. Additional symptoms were noted and recorded if observed.

Patient outcome

Throughout the three-week admission, GF scored very little on the withdrawal scale and completed the detoxification programme relatively comfortably. The rating scale assessed physical symptoms of withdrawal including gastric upset, changes in autonomic nervous system activity (e.g., sweating and blood pressure) and tremor, as well as psychological symptoms including anxiety, restlessness and irritability. GF scored 0 or 1 on these measures throughout the detoxification, equivalent to symptoms being absent or of mild intensity. On an interview prior to discharge, she remarked that she was pleased with her admission and was

motivated to remain abstinent. When asked subjectively about her memory impairment and asked to score her memory now and prior to the admission, she rated herself as 7 and 2 (out of 10), respectively. Her main concern was an uncomfortable feeling of restlessness and inability to remain seated and a marked tremor in her legs and hands. The Parkinsonian tremor responded well to trihexyphenidyl 5 mg up to three times daily, taken as required, which was increased after a moderate improvement with 2 mg. The restlessness (akathisia) remained pronounced so her lorazepam 2 mg was converted to diazepam 5 mg morning and evening and 10 mg at night. This resulted in an objective improvement in her ability to remain seated and subjective reports of calmness. A follow-up appointment for review of her psychotropic medication was arranged with her local community mental health team, as this was not within the remit of the inpatient detoxification unit. Nevertheless, a change in the antipsychotic regimen in order to minimize extra-pyramidal side effects (EPSE) and a subsequent reduction in trihexyphenidyl and diazepam doses would help to reduce the risk of GF misusing these compounds in the future. She was discharged from the inpatient detoxification unit as planned and had not relapsed at six months.

Discussion

This case fulfils the DSM-IV criteria for substance misuse, with GF exhibiting tolerance, drug-seeking behaviour, continuing use despite adverse effects and withdrawal reactions. Perhaps, the *prima facia* reason for abuse would be tolerance to the antihistaminic H_1-receptor-mediated sedative effects of DPH, resulting in dose escalation to achieve the desired hypnotic effect. However, it is also notable that GF described insomnia or 'a buzz' associated with her use of higher doses of DPH. This may be due to activation of the mesolimbic dopaminergic system, leading to rewarding effects and drug-seeking behaviour (Yeomans, 1995). It is not clear whether DPH posses any direct stimulatory effects on the dopaminergic system. In common with GF, the other reported case reports of DPH misuse had a diagnosis of schizophrenia and were prescribed antipsychotic medication. The adverse effects of antipsychotics are well documented and EPSE are reported in many patients receiving typical antipsychotics. The most common pharmacological treatment strategy for managing EPSE is prescription of antimuscarinic medication, such as procyclidine or trihexyphenidyl. Vinson (2003) found that 10 mg DPH administered intravenously rapidly resolved prochlorperazine induced akathisia and may be a treatment option for severe akathisia. It is therefore possible that GF along with the patients in other case reports were using DPH to self-medicate against EPSE.

Although GF scored little on the DPH withdrawal scale during detoxification, she did describe symptoms of restlessness consistent with the case report of Feldman and Behar (1986). Commenting on this case, it was hypothesized that withdrawal symptoms could be ascribed to cholinergic rebound, in particular, the irritability and insomnia that resembled an akathisia-like syndrome (Glickman, 1986). Although cholinergic rebound may account for a proportion of the symptoms, the author makes no reference to the patient's treatment with the typical antipsychotic thiothixane. The 34-year-old man had previously been prescribed trihexyphenidyl, and therefore was presumably experiencing EPSE. On assessment, the symptoms GF described during detoxification were deemed withdrawal emergent EPSE, associated with co-prescribed antipsychotic medication. GF was taking an antipsychotic dose equivalent to over 1.5 g of chlorpromazine per day (Atkins *et al.*, 1997). The large dose of antipsychotic medication co-prescribed for GF and her subjective view that DPH improved EPSE present a possible rationale for DPH misuse in this case. However, the possible association between DPH abuse and psychotic illness or antipsychotic medication suggested in this paper must be viewed with some caution. Although self-medication for EPSE may account for a percentage of the cases reported, the relatively widespread nature of the problem of DPH misuse perceived by community pharmacists suggests that it is unlikely to result exclusively from patients treated with antipsychotic medication attempting to reduce the severity of EPSE. Similarly, many cases of DPH misuse arising from the use of escalating doses to treat insomnia probably remain under-reported. Patients with psychiatric illnesses may be monitored more closely than the general population; hence any co-morbid conditions are more likely to be detected. This report provides further evidence that DPH abuse can present in patients with psychiatric comorbidity, perhaps due to a combination of its anti-parkinsonian properties and euphoric and stimulant effects.

Conclusion

DPH abuse is cited in the literature. The cases described above make few references to previous reports while making similar recommendations regarding the possible increased abuse potential of DPH if co-prescribed with antipsychotics. The case report highlights the importance of enquiring about non-prescribed medication when taking a drug history. Similarly, community pharmacists or GPs should be vigilant to excessive requests for DPH, particularly in patients with a psychotic illness or those prescribed antipsychotic medication, and be prepared to direct patients for treatment accordingly. To the best of our knowledge, this is the first review of the published data and the only well-documented treatment plan that has resulted in a successful detoxification with continuing abstinence.

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