The Importance of Taking a History of Over-the-Counter Medication Use: A Brief Review and Case Illustration of “PRN” Antihistamine Dependence in a Hospitalized Adolescent

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Abstract

Over-the-counter (OTC) and prescription medication abuse has been rapidly increasing, yet publications on OTC abuse in adolescents are limited. We present a brief literature review and a novel report of antihistamine dependence emerging after admission in an adolescent, subsequently treated with naltrexone. This case highlights the need to take a thorough history of OTC, herbal, and prescription drug use from parents and patients separately and repeatedly, at initial presentation, and again if withdrawal symptoms emerge. General strategies for combating OTC and prescription abuse are given.

Introduction

KNOWN AS “PHARMING,” prescription and over-the-counter (OTC) medication abuse is of significant concern in adolescents. In 2005, nearly 20% of teens in grades 7–12 reported abusing prescription medication to “get high”; 10% abused cough syrup (Partnership for a Drug-Free America, 2005). Data on OTC abuse separate from prescription drug abuse are difficult to find, but over one in six clients of the Tulare County, California, Drug Court admitted to abusing OTC medications, primarily ephedrine (Lessenger et al. 2000). Lifetime misuse of OTC cough/cold medications was ~4% in adolescents and young adults surveyed as part of the 2006 National Survey on Drug Use and Health (Ford 2009). Correlated factors included older age, lower income, other substance abuse, poorer physical health, and depression. Emergency room visits for nonmedical use of prescription and OTC medications are now as common as those resulting from illegal drug abuse (CDC 2010). OTC drugs used by those presenting to emergency departments for drug treatment include aspirin, cough syrup, diphenhydramine (DPH) and other antihistamines, and sleep aids (National Survey on Drug Use and Health 2004). Recent national legislative attention has focused on OTC medication abuse; the Dextromethorphan Abuse Reduction Act of 2009, S. 1383, is currently under review by the senate judiciary subcommittee (www.govtrack.us/congress/bill.xpd?bill=s111-1383). This review highlights antihistamines, easily obtained but less commonly expected as an OTC medication of abuse, which confounded inpatient psychiatric treatment in a case described below where history of antihistamine abuse was not elicited or disclosed.

Antihistamines are easily accessible medications, usually sold OTC to treat allergic reactions, pruritus, or peripheral vertigo. Their sedating effects have led to usage as a sleep aid or an anxiolytic, often by child and adolescent mental health practitioners, particularly in acute inpatient psychiatric hospital settings (Kaplan and Busner 1997). Although widely used and generally considered safe, cases of antihistamine abuse and dependence, especially of DPH, have been described in the medical literature (Thomas et al. 2009). Those misusing antihistamines have listed calming effects (Cox et al. 2001), mild euphoria (Feldman and Behar 1986), and ability to stop tremors (Thomas et al. 2009) as desired effects. Antihistamines, most frequently DPH, are also used recreationally for hallucinogenic effects, at doses of 300–700 mg (Radovanovic et al. 2000). Reported cases of DPH dependence have resulted from usage of large doses (often over 1,000 mg per day) over periods of months or years (Thomas et al. 2009), usually in adult males, often those with schizophrenia who are taking antipsychotics. Thomas et al. (2009) speculate that DPH abuse may occur in those patients with psychiatric comorbidity and antipsychotic treatment, because of the combination of antiextrapyramidal, euphoria, and stimulant effects. Withdrawal symptoms listed in the literature include worsening of insomnia, rhinorrhea, nausea, irritability, restlessness, abdominal cramps, sweating, and diarrhea (Feldman and Behar 1986; de Nesnera 1996). Gradual tapering has been the only described detoxification treatment plan, which appears to alleviate the withdrawal symptoms (Thomas et al. 2009).

The purpose of this article was to encourage providers to ask routinely about prescription and OTC nonmedical use. Here, we

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report a case of possible rapid onset antihistamine dependence in an adolescent girl with a history of opioid dependence, with no antipsychotic coprescription, who then appeared to benefit from the addition of naltrexone during the course of detoxification.

Case Illustration

A 15-year-old girl was admitted to a regional urban inpatient adolescent psychiatric unit for worsening depressive symptoms leading to suicidal ideation and self-injurious behavior (cutting). She had met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria as an outpatient for bipolar disorder type II and anxiety disorder, not otherwise specified, and was prescribed duloxetine and sertraline at the time of admission. Recent attempts by her outpatient psychiatrist to taper down her duloxetine resulted in complaints of worsening anxiety. She had just begun outpatient substance abuse treatment for cannabis dependence and alcohol abuse. She also had been admitted the previous year for a 2-week inpatient detoxification after she became dependent on an opioid (an oxycodone/acetaminophen preparation) within several months, prescribed for treatment-resistant headaches. Her urine toxicology screen was negative on admission for common substances of abuse. Family history was remarkable for mood disorders and opioid dependence. On admission, along with her antidepressants, hydroxyzine 25 mg by mouth every 8 hours was ordered as an "as-needed" (PRN) medication for her anxiety symptoms. She quickly consistently utilized this, stating that it helped with her anxiety symptoms. She learned to maximally utilize this medication within 4 days of admission, asking for a new dose at the next scheduled time allowed, and began advocating for an increased dose. On hospital day 5, the dose was increased to 50 mg by mouth every 8 hours. Within 48 hours, she began maximally utilizing this as well as requesting for an intramuscular DPH dose, stating that these were the only things that helped with her anxiety. She did not appear classically anxious according to unit staff and also did not report symptoms typically associated with anxiety as defined by DSM-IV. Because of primary concerns of drug-seeking behavior with apparent tolerance developing to hydroxyzine, she was discouraged daily by unit staff from using hydroxyzine and encouraged to use cognitive-behavioral coping strategies instead, which

met significant resistance from the patient. The patient's mother then revealed that the patient had been ingesting significant amounts of DPH at home. Mother reported frequently giving her a DPH preparation up to the maximum daily dose (400 mg/day), but also finding an empty box of this medication in the patient's room on one occasion.

On hospital day 14, a plan was put into place to taper the hydroxyzine, although this decision was strongly opposed by the patient. After much negotiation, it was decided to implement an alternating dose of 50 and 25 mg every 6 hours, as a gradual taper. The PRN dose of intramuscular Benadryl was discontinued. She subsequently exhibited mild nausea, significant nasal congestion, throat discomfort, and irritability and made increased demands for medication beginning the same day. Her systolic blood pressure and heart rate were also slightly higher but returned to her baseline on the following day. The patient's mother also had difficulty tolerating the taper and contributed to drug-seeking by asking to have the on-call physician paged during the night to request her daughter be given DPH for her "upper respiratory infection," despite repeated explanation of withdrawal symptoms. On day 16, the nausea, but not the other symptoms, resolved. The patient continued to exhibit significant drug-seeking behavior as well as irritability and difficulty concentrating. On day 16, because of the similarity between her current withdrawal symptoms and those of opioids, an oral naltrexone trial was initiated, with the possibility that there might also be beneficial effects on self-injurious behavior (Smith et al. 1995, Symons et al. 2004). Within a day of the initial dose of oral naltrexone of 25 mg, the patient reported improved nasal congestion and irritability. Drug-seeking behavior decreased significantly, and by 2 days later, on day 18, she no longer utilized the maximal PRN doses, for she "no longer felt the need." She did continue to have mild nasal congestion in the mornings and at night. Naltrexone dose was gradually increased to 75 mg per day over the 5 days. Figure 1 outlines the course of her antihistamine use; vasomotor instability appears present prior to and especially during withdrawal symptoms, with stabilization on adding naltrexone. Her urges of cutting, which had been a daily concern, also alleviated, and on day 21, she did not request any hydroxyzine dose. She further reported that she no longer had the urges to cut, that her mood had significantly improved, and that she felt "real," capable of fully experiencing the "present moment."

FIG. 1. Hydroxyzine use over the course of hospitalization. * Intramuscular diphenhydramine administration. HR = heart rate (beats per minute); SBP = systolic blood pressure (mmHg). A color version of this figure is available in the online article at www.liebertonline.com.

Discussion

Our patient's chronology of events, symptoms consistent with previously documented cases of antihistamine withdrawal, and behaviors fulfilling DSM-IV criteria for substance dependence (tolerance, increasing usage, drug-seeking behavior, and withdrawal reactions) point to antihistamine dependence and subsequent withdrawal. We believe this to be the first case report of antihistamine dependence in an adolescent girl. Additionally, it may be the first report of use of naltrexone to mitigate antihistamine withdrawal symptoms. It is not entirely clear if the patient rapidly developed hydroxyzine dependence during the first part of her hospital course, or if she was admitted with a preexisting dependence, with the full extent of at-home OTC DPH use unknown and possibly greater than reported. Arguing for this is the presence of vasomotor instability seen early in the hospital course (Fig. 1). The extent and duration of her DPH abuse prior to admission was likely in the order of weeks, and not in very high dose as reported in previously described cases. Further, once she was admitted to the unit, her hydroxyzine dose never exceeded the daily maximum dosage of 400 mg per day (her highest daily dose was 200 mg). Her personal history of opioid dependence and strong family history for addiction (mother with history of opioid dependence, father with multiple substance dependence including heroin) may have predisposed her to become physiologically dependent on antihistamines, despite relatively low dosage and a relatively short time course of usage. With recent findings of antihistamines' pharmacologic effects as similar to cocaine and described reinforcing effect of antihistamines with cocaine, we speculate that her opioid-experienced mesolimbic pathways had a heightened susceptibility to antihistamine dependence. It is also possible that given her personal and family history of substance dependence, she might have obtained reinforcement from any PRN medication with central nervous system effects.

Although it is probable that naltrexone quickly reduced her cravings, they may have cleared because of a natural time course. Arguing against this is the abrupt drop in dose utilization. It is possible that, given proposed stimulatory effects of select antihistamines on dopamine transmission in the mesolimbic pathways (Tanda et al. 2008), naltrexone is also effective in diminishing the desired effects created by antihistamines that lead to misuse. Some of the neurochemical basis for such abuse potential has been uncovered. Antihistamines primarily act as antagonists at histamine H1 receptor, although they have antagonistic properties at the five muscarinic cholinergic receptors (Bolden et al. 1992). Some H1 histamine antagonists, in this case DPH and chlorpheniramine enantiomers, stimulate dopamine transmission in the nucleus accumbens, part of the mesolimbic "reward" pathway, in rats, much like cocaine (Tanda et al. 2008). This effect is thought to be mediated by properties other than antihistamine's action on histamine H1 receptors. Especially important to the case described below, combined reinforcing effects of opioids (specifically cocaine) and antihistamines have also been described in epidemiological studies as well as in animal studies. For example, a *Epidemiologic Trends in Drug Abuse Advance Report* (2006) indicated an abuse of a combination of heroin and DPH (called "cheese"), and also DPH misuse has been described in patients prescribed methadone (Roberts et al. 1999). This reinforcing effect was confirmed and quantified in a controlled environment using rhesus monkeys (Banks et al. 2009), although the neurochemical basis of such reinforcing effects remained a mystery.

Clinical variables associated with OTC medication abuse include being Caucasian, female, younger, having a history of opiate

use, and using concomitantly with alcohol, including in suicide attempts (Drug Abuse Warning Network 2006). The patient presented here appears to meet nearly all of these descriptors.

General strategies for psychopharmacologic provider prevention and management of prescription and OTC substance abuse consist of (1) routinely asking about nonmedical prescription, herbal, and OTC medication use at initial appointments and at changes in mental status; (2) monitoring for illegal drug use, which may be a "gateway" to OTC abuse for some; (3) providing medication disposal containers on site for unused/unwanted medications; (4) educating parents and adolescents about potential negative effects of nonmedical use, "sharing," and abuse of OTC and prescription drugs; (5) advising and documenting family storing practices and monitoring of available pharmaceuticals in the home; (6) keeping accurate and timely records of prescription refills and controlled substance forms; and (7) early referral for assessment, detoxification, and substance abuse treatment for those patients suspected of abuse and addiction of prescription or OTC products (Levine 2007; Lessenger and Feinberg 2008).

In summary, with respect to the specific case presented above, antihistamines may have significant abuse potential in adolescents, as they are widely accessible and considered relatively safe. With the restriction of sales for pseudoephedrine and ease of access to OTC substances such as antihistamines and dextromethorphan as potential agents of abuse, healthcare professionals must be aware of the potential for misuse in the general adolescent population. Despite little documented efficacy, antihistamines remain in widespread use also with high safety perception as a "PRN" medication of choice on child and adolescent inpatient psychiatric units. Our case underscores the importance of avoiding their use in patients with past or current opioid dependencies and of close monitoring of effects in patients with family histories of opioid abuse. Our patient's withdrawal symptoms resembled those of opioids and the addition of naltrexone appeared to significantly alleviate both cravings associated with the detoxification process as well as her initial target symptoms of urges to self-harm. This case also emphasizes the importance for all healthcare professionals who take medication histories to specifically inquire about patients' OTC drug usage, interviewing both parents and adolescents separately and repeatedly if clinically indicated. Further study and description of similar cases will result in improvements in clinical care for child and adolescent patients at high risk for opioid and/or antihistamine dependence.

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