A 10-Year Retrospective Pilot Study of Parenteral Diphenhydramine Use in Home Infusion Patients

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ABSTRACT

Introduction

Patients who administer chronic parenteral diphenhydramine are at risk of developing behavioral issues that may represent misuse or abuse. The purpose of this study was to assess potential risk factors and comorbidities for medication noncompliance in the home infusion patient population prescribed parenteral diphenhydramine.

Methods

The study was a retrospective review of the patient population prescribed parenteral diphenhydramine from 2010 to 2020. Data collected from the electronic health record included age, gender, race, indication, type of specialty practice prescribing, duration of therapy, prior history of oral diphenhydramine use, reason for discontinuation, comorbidities, and concomitant medications. Comorbidities assessed included chronic pain, tobacco use, alcohol use, psychiatric disorders, venous access device infections, history of venous thromboembolism, documented overdoses, and history of drug abuse.

Results

Between 2010 and 2020, 101 patients were prescribed scheduled parenteral diphenhydramine. After exclusions, the study group contained 76 patients who met the inclusion criteria. Noncompliance was documented in 27 patients (35.5%). Noncompliance was associated with a diagnosis of mast cell disorder (25.9%) and nausea and vomiting (44.4%). Comorbidities associated with noncompliance included chronic pain (88.9%) and psychiatric disorders. The age range for the compliant group was 20-69 and the noncompliant group was 20-49. Noncompliance was more common in females than males in the study.

Conclusion: The analysis of this patient population supports patients showing signs of parenteral diphenhydramine misuse tend to have higher rate of comorbidities associated with substance use disorders when the duration of therapy was 3 months or longer.

Keywords: *Diphenhyrdramine, abuse, noncompliance, infusion, intravenous, Benadryl®*

Introduction

The abuse of prescription drugs in the United States has reached an epidemic level.[1] In 2012, the National Survey on Drug Use and Health found that more than 16.7 million people (12 years and older) in the U.S. abused prescription drugs and concluded that approximately 2.1 million people met the criteria for a Substance Use Disorder related to prescription drugs. This represented a 250% increase in prescription drug abuse over the previous 20 years.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines drug abuse as a Substance Use Disorder (SUD) when a patient presents with at least 2 of 11 predefined criteria (see Table 1).[2]

There are many case studies of diphenhydramine abuse and withdrawal in literature searches.[3,4,5] Most case studies involve the abuse of over-the-counter (oral) diphenhydramine. Surveys of pharmacists conducted in Great Britain showed that half or more suspected that diphenhydramine and other sedating antihistamines are subject to misuse.[6,7] There is little clinical information available about the diagnosis, prevention, and treatment of diphenhydramine abuse. In general, patients with a SUD are at a higher risk of being diagnosed with depression, bipolar disorder, anxiety, post-traumatic stress disorder (PTSD), eating disorders, schizophrenia, and attention deficit hyperactivity disorder (ADHD).[8] Risk factors specific to sedative-hypnotic prescription drug abuse include white race, female sex, being uninsured, being unemployed, panic symptoms, other psychiatric symptoms, alcohol abuse, or dependence, cigarette use, illicit drug use, and history of intravenous drug use.[9]

Diphenhydramine is an antihistamine with anticholinergic and sedative side effects. It competes with histamine for H1-receptor sites in the gastrointestinal tract, blood vessels, and respiratory tract. Side effects of diphenhydramine include tachycardia, blurred vision, urinary retention, constipation, anorexia, diaphoresis, xerostomia, central nervous system depression, sedation, dizziness, agitation, confusion, and psychosis. The potential for misuse appears to be related to elevating mood, increasing energy levels, and euphoria.[3,4] There may also be increases in dopaminergic neurotransmission along pathways that affect the reward system.[3] Patients with schizophrenia or other psychiatric conditions may experience a reversal of secondary negative symptoms associated with antipsychotic medications (such as lack of motivation, flattened affect, and social withdrawal) when taking diphenhydramine due to its anticholinergic effects, further enhancing the risk of abuse.[3]

A small subset of patients who are prescribed diphenhydramine infuse the drug parenterally. For patients that require ongoing administration of parenteral (primarily intravenous, IV) diphenhydramine, home infusion companies can provide patients with the medication and supplies needed to infuse in the home setting. Because this applies to a small number of patients, there is a scarcity of information for dosing and managing them. The risk of SUD related to

TABLE 1 | DSM-5 diagnostic criteria for Substance Use Disorder (SUD)[2]

A problematic pattern of use leading to clinically significant impairment or distress is manifested by 2 or more of the following within a 12-month period:

1. Often taken in larger amounts or over a longer period than was intended
2. A persistent desire or unsuccessful efforts to cut down or control use
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects
4. Craving or a strong desire or urge to use the substance
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects
7. Important social, occupational, or recreational activities are given up or reduced because of use
8. Recurrent use in situations in which it is physically hazardous
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance
11. Withdrawal

diphenhydramine has the potential to be especially problematic in the home infusion population when the IV route is utilized, given that this route results in rapid drug bioavailability and is the most efficient route to produce euphoria for many drugs.

An example of an indication that may require chronic parenteral diphenhydramine treatment is Mast Cell Activation Syndrome (MCAS). MCAS includes a heterogeneous group of disorders characterized by the release of mast cell mediators. The disorders are generally considered incurable. Mast cells contain more than 200 mediators, including histamine and tryptase, which contribute to their immune-related and non-immune functioning.[10] When activated, mast cells release these mediators, which can result in the signs and symptoms of an allergic reaction which are present in many mast cell disorders. First-line therapies for MCAS include avoidance of triggers and treatment of symptoms. Patients who experience anaphylactic reactions may require epinephrine, steroids, and antihistamines to control symptoms.[10]

One study of patients with MCAS found that infusing diphenhydramine continuously at 10-14.5 mg/hr appeared safe and effective, and reduced disease flares.[11] The study was performed in 10 patients with life-threatening MCAS (aged 18-49; 9 were women) who experienced continuous anaphylactoid or severely dysautonomic flares. At baseline they were treated with subcutaneous epinephrine, H2-Blockers, and intermittent diphenhydramine. Baseline dosing of diphenhydramine among patients was 600-800 mg per day in divided doses (an average of 25-33 mg/hr) administered via IV, intramuscular, or oral routes. All were hospitalized for essentially continuous anaphylaxis and were started on continuous diphenhydramine infusion (CDI) while inpatient. CDI was initially started at 5 mg/hr IV. A rescue dose of diphenhydramine 25-50 mg IV was given with each disease flare, along with an increase of CDI by 1-2 mg/hr. One patient stopped CDI due to reaching 17 mg/hr without effect. Other patients were stabilized on 10-14.5 mg/hr, with a reduction in flare severity and a reduction of flare frequency to 1-4 times per month. Stabilized patients ceased continuous flares within 24 hours and were discharged home on CDI with ambulatory pumps within 48 hours. In the home setting they had diphenhydramine 10-25 mg IV available as needed for flares. Patients were followed for 0.5-21 months with continued reduction in flares (1-4 times per month). The author of the study reported no evidence of tolerance or waning of effect during follow up.[11]

It is the experience of pharmacists at a regional home infusion provider that the patient population is at risk of developing behavioral issues with chronic parenteral diphenhydramine that may represent misuse or abuse. Aside from the MCAS study above, there is little information available to guide clinicians on the optimal dosing of outpatient chronic parenteral diphenhydramine. In addition, there is a lack of clinical information and guidance of the risk factors for and treatment of diphenhydramine abuse. Therefore it was decided to conduct a retrospective analysis of our patient population to determine next steps.

Purpose

To review the patient population who were prescribed parenteral diphenhydramine from 2010 to 2020 in order to assess potential risk factors or comorbidities associated with noncompliance. To assess the direction of future research in the area of SUD related to chronic parenteral diphenhydramine use.

The purpose of this study was not to diagnose drug abuse or SUD.

Methods

In the first quarter of 2021, the pharmacists conducted a retrospective review of patients who had been prescribed scheduled parenteral diphenhydramine (predominantly intravenous) from 2010 to 2020. Patients of all ages were included if any doses were dispensed to them during that time period. Patients were excluded if they only received oral diphenhydramine, if diphenhydramine was prescribed as a premedication for an intermittent specialty medication (ex: prior to intermittent infliximab infusions), or if it was dispensed as part of an anaphylaxis kit.

Data collected included age at start of treatment with parenteral diphenhydramine, gender, race, indication, type of specialty practice prescribing, duration of therapy, prior history of taking oral diphenhydramine, and reason for discontinuation. Comorbidities assessed included chronic pain, tobacco use, alcohol abuse, various psychiatric disorders, history of line infections, history of venous thromboembolism, documented overdoses, and history or family history of drug abuse. Concomitant medication drug classes were also assessed.

Because of the retrospective nature of this study and the limited diagnostic information available, few criteria

used in the diagnosis of SUDs could be evaluated (see Table 1).[2] Rather than trying to diagnose abuse or a SUD, the pharmacists collected information about patient noncompliance that indicated misuse for this pilot study.

For the purpose of our study, noncompliance was defined as meeting at least one of the following criteria: documentation in the patient electronic medical record of more than 1 early refill request; the documented intervention of a home infusion clinician related to problems with diphenhydramine therapy; necessity of a compliance contract related to diphenhydramine noncompliance; documentation in an alerts field of noncompliance or early refills; other documentation in the electronic medical record stating the prescriber was aware of noncompliance. For this study, patients will be referred to as "noncompliant" if they met any of the criteria above, and will be labeled as "compliant" if they did not have documentation of noncompliance as above.

Institutional Review Board (IRB) Status

The research involved secondary data analysis where the data set was deidentified before analysis and recorded in a manner where the resulting data contained no information that could be linked directly or indirectly to the identity of the subjects.

Results

Between 2010 and 2020, 101 patients were prescribed scheduled parenteral diphenhydramine. After excluding patients as described above, 76 met inclusion criteria (see Table 2). After data collection and analysis, 49 patients (64.5%) were determined to be compliant and 27 (35.5%) patients had documentation of noncompliance. Of the 76 total patients, 58 (76.3%) were female, 17 (22.4%) were male, and 1 (1.3%) was transgender. Of the patients who had documentation of noncompliance, 24 (88.9%) were female and 3 (11.1%) were male. The majority of compliant patients

TABLE 2 | Patient Demographics

	All Patients, n=76	Compliant, n=49	Noncompliant, n=27
	n(%)	n(%)	n(%)
Total Patients	76 (100%)	49 (64.5%)	27 (35.5%)
Sex			
Male	17 (22.4%)	14 (28.6%)	3 (11.1%)
Female	58 (76.3%)	34 (69.4%)	24 (88.9%)
Transgender (F to M)	1 (1.3%)	1 (2.0%)	0
Age*			
0-9	4 (5.3%)	4 (8.2%)	0
10-19	3 (3.9%)	3 (6.1%)	0
20-29	15 (19.7%)	8 (16.3%)	7 (25.9%)
30-39	16 (21.1%)	8 (16.3%)	8 (29.6%)
40-49	17 (22.4%)	9 (18.4%)	8 (29.6%)
50-59	11 (14.5%)	8 (16.3%)	3 (11.1%)
60-69	8 (10.5%)	7 (14.3%)	1 (3.7%)
70-79	1 (1.3%)	1 (2.0%)	0
80-89	0	0	0
90-99	1 (1.3%)	1 (2.0%)	0
Race			
Native American	1 (1.3%)	0	1 (3.7%)
Black/African American	1 (1.3%)	1 (2.0%)	0
Hispanic or Latino	2 (2.6%)	1 (2.0%)	1 (3.7%)
White (Non-Hispanic, Non-Latino)	64 (84.2%)	40 (81.6%)	24 (88.9%)
Unknown	8 (10.5%)	7 (14.3%)	1 (3.7%)

*Age at start of treatment with parenteral diphenhydramine

FIGURE 1 | Percentage of Noncompliant Patients by Age Range (n=27)

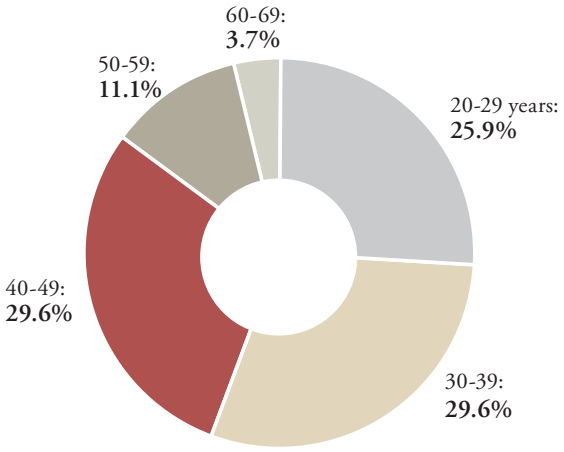


TABLE 3 | Indication for Parenteral Diphenhydramine Therapy

	All Patients, n = 76	Compliant, n = 49	Noncompliant, n = 27
Abdominal pain, n (%)	1 (1.3%)	0	1 (3.7%)
Anti-infective premedication, n (%)	27 (35.5%)	23 (46.9%)	4 (14.8%)
End of Life Care and Comfort, n (%)	8 (10.5%)	7 (14.3%)	1 (3.7%)
Idiosyncratic anaphylactoid events, n (%)	1 (1.3%)	0	1 (3.7%)
Itching, n (%)	2 (2.6%)	2 (4.1%)	0
Mast Cell Disorder, n (%)	9 (11.8%)	2 (4.1%)	7 (25.9%)
Nausea/vomiting (+/- itching), n (%)	27 (35.5%)	15 (30.6%)	12 (44.4%)
Rash, n (%)	1 (1.3%)	0	1 (3.7%)

fell into a wide range of age groups from age 20 to 69, while noncompliant patients were mostly concentrated between the ages of 20 and 49 (see Figure 1). Given the small numbers of patients who were non-white, we were unable to assess trends based on race.

The most common indications for parenteral diphenhydramine therapy for all patients were anti-infective premedication and nausea/vomiting (see Table 3). A higher percentage of compliant patients had an indication of anti-infective premedication vs. noncompliant patients ([n=23, 46.9%] vs. [n=4, 14.8%]). A higher percentage of noncompliant patients vs. compliant patients had an indication of mast cell disorder ([n=7, 25.9%] vs. [n=2, 4.1%]) and nausea/vomiting ([n=12, 44.4%] vs. [n=15, 30.6%]).

When analyzing comorbidities (see Table 4), noncompliant patients tended to have chronic pain more frequently than compliant patients ([n=24,

TABLE 4 | Comorbidities

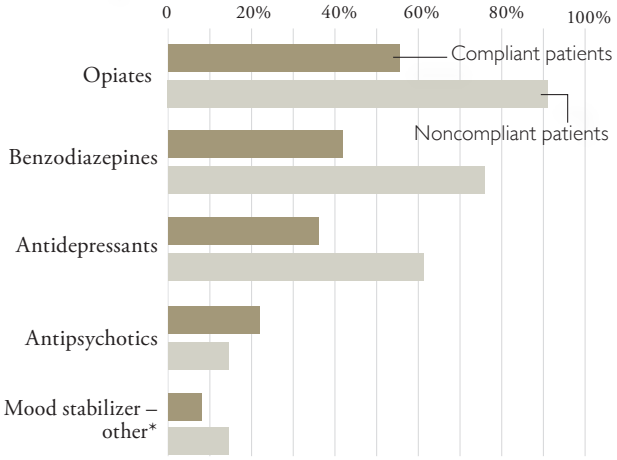
	All Patients, n=76	Compliant, n=49	Noncompliant, n=27
	n(%)†	n(%)†	n(%)†
Chronic Pain	50 (65.8%)	26 (53.1%)	24 (88.9%)
Tobacco Use (Past or Present)	18 (23.7%)	11 (22.4%)	7 (25.9%)
Alcohol Abuse	3 (3.9%)	2 (4.1%)	1 (3.7%)
Anxiety	30 (39.5%)	15 (30.6%)	15 (55.6%)
Depression	33 (43.4%)	17 (34.7%)	16 (59.3%)
Bipolar Disorder	4 (5.3%)	3 (6.1%)	1 (3.7%)
ADHD	6 (7.9%)	2 (4.1%)	4 (14.8%)
Eating Disorder	3 (3.9%)	1 (2.0%)	2 (7.4%)
PTSD	9 (11.8%)	4 (8.2%)	5 (18.5%)
Schizophrenia	2 (2.6%)	1 (2.0%)	1 (3.7%)
History Line Infections	10 (13.2%)	3 (6.1%)	7 (25.9%)
History VTE	29 (38.2%)	16 (32.7%)	12 (44.4%)
Documented Overdoses	1 (1.3%)	1 (2.0%)	0
History of Drug Abuse*	4 (5.3%)	2 (4.1%)	2 (7.4%)

ADHD = Attention Deficit Hyperactivity Disorder, PTSD = Post-traumatic Stress Disorder, VTE = Venous Thromboembolism

*History of Drug Abuse = self-history or family history

† Patients may have more than 1 comorbidity

FIGURE 2 | Concomitant Medications: Compliant vs. Noncompliant Patients (n=76)



* clonidine, divalproex, lamotrigine, lisdexamfetamine, and topiramate

88.9%] vs. [n=26, 53.1%]). Noncompliant patients had higher rates of psychiatric disorders except for bipolar disorder ([n=1, 3.7% for noncompliant] vs. [n=3, 6.1% for compliant]). Noncompliant patients had rates of anxiety and depression that were more than 20% higher than compliant patients ([n=15, 55.6%] vs. [n=15, 30.6%] for anxiety, and [n=16, 59.3%] vs. [n=17, 34.7%] for depression). A history of PTSD was identified in 18.5% (n=5) of noncompliant patients vs. 8.2% (n=4) of compliant patients. Noncompliant patients tended to have higher rates of history of venous thromboembolism (VTE) compared to compliant patients ([n=12, 44.4%] vs. [n=16, 32.7%]). There was a history of line infections in 25.9% (n=7) of noncompliant patients, compared to 6.1% (n=3) of compliant patients. Due to low incidences, it was not feasible to see trends in documented overdoses or history of drug abuse.

Patients were evaluated for the concomitant use of opiates, benzodiazepines, antidepressants, antipsychotics, and other mood stabilizers during parenteral diphenhydramine therapy (see Figure 2). The difference in prescribing of opiates for noncompliant vs. compliant patients was 35.5% ([n=25, 92.6%] vs. [n=28, 57.1%]), for benzodiazepines 34.9% ([n=21, 77.8%] vs. [n=21, 42.9%]), and for antidepressants 26.3% ([n=17, 63.0%] vs. [n=18, 36.7%]). Despite literature stating that patients taking antipsychotics may have an increased risk of diphenhydramine abuse due to the reversal of symptoms associated with antipsychotic medications, our patient population showed a decreased rate of antipsychotic use in noncompliant patients; this may be confounded by the small patient population studied (compliant [n=11, 22.4%], noncompliant [n=4, 14.8%]).[2] Patients were additionally evaluated for taking medications associated with SUD, such as buprenorphine, naloxone, and buprenorphine/naloxone. It was not feasible to assess differences in the use of these medications in this patient population due to low numbers (2 compliant patients, 2 noncompliant patients), and the concern that this information may not be useful due to prescribing practices in some specialties such as the practice of prescribing naloxone to patients taking opiates regardless of assessed risk of overdose.

There appears to be a strong correlation between duration of parenteral diphenhydramine therapy and compliance, as defined in this study (see Table 5). The majority of compliant patients had a duration of therapy of less than 2 weeks (n=20, 40.8%), while the majority of noncompliant patients were on parenteral diphenhydramine for greater than 3 months (n=23, 85.2%).

TABLE 5 | Duration of Parenteral Diphenhydramine Therapy

	All Patients, n=76	Compliant, n=49	Noncompliant, n=27
	n(%)	n(%)	n(%)
< 2 weeks	21 (27.6%)	20 (40.8%)	1 (3.7%)
2 weeks to 1 month	10 (13.2%)	9 (18.4%)	1 (3.7%)
1 - 2 months	3 (3.9%)	3 (6.1%)	0
2 - 3 months	5 (6.6%)	3 (6.1%)	2 (7.4%)
> 3 months	37 (48.7%)	14 (28.6%)	23 (85.2%)

Discussion

The results of this study reveal trends in the patient population, but based on the small sample size, significance differences can not be calculated. Furthermore, the correlations presented do not prove causation. Without further analysis and formal diagnosis, it is not possible to determine whether the noncompliance seen in these patients represents a SUD, or if the patients are exhibiting drug seeking behavior due to inadequate treatment of their underlying disease.

Unfortunately, there are no guidelines for the management of patients prescribed chronic diphenhydramine therapy. Other drug therapies, such as opiates, have guidelines available to direct prescribers on baseline patient evaluations (including benefit-to-harm analysis), obtaining informed consent (including education about goals, expectations, risks and alternatives), guidance on dosing and titration, patient monitoring, protocols for patients with history of drug abuse or psychiatric issues, managing adverse events, potential adjunctive therapies, driving and work safety, implications in pregnancy, the need for an identified managing provider, and guidance on when a specialist consult is needed.[12] General practices to reduce the risk of drug misuse include starting with the lowest possible dose, titrating doses slowly, and limiting the duration of therapy if possible. Early refills should be avoided.[12]

Despite having risk factors for SUD, some patients require treatment with medications that have abuse potential. Treatment with diphenhydramine is often necessary for the treatment of intractable vomiting or mast cell disorders. Guidelines are needed to direct clinicians on how to best manage these patients.

Limitations of this study include a small patient population and limited clinical documentation. Because of the lack of understanding about the potential for the misuse of parenteral diphenhydramine, these patients were not evaluated for diphenhydramine-related SUD by their providers in almost all cases. The retrospective nature of this study excluded patient interviews or requests for additional documentation from referring providers. The authors of this study acknowledge that based on the established definitions of compliant and noncompliant and the clinical information available, it cannot be concluded that noncompliant patients misused or abused diphenhydramine therapy.

Conclusions

The analysis of this patient population supports that patients showing signs of parenteral diphenhydramine misuse tend to have higher rates of many of the comorbidities associated with SUD (depression, anxiety, PTSD, eating disorders, schizophrenia, and ADHD).[8] They also had higher rates of multiple risk factors for sedative-hypnotic prescription drug abuse (especially female sex and psychiatric symptoms).[9] In addition, patients tended to be younger adults (aged 20 to 49); they had higher rates of chronic pain; and they had higher rates of line infections. Medication assessment revealed higher rates of opiate, benzodiazepine, and antidepressant use. The most common indications for parenteral diphenhydramine in this patient subset were mast cell disorders and nausea/vomiting, and the duration of therapy was greater than 3 months in most cases.

Further research and guidance regarding chronic parenteral diphenhydramine use in the home setting is needed. Research and guidance should include analysis of larger patient populations, risk factors for diphenhydramine misuse, benefit-to-harm analysis, optimal dosing and titration, patient monitoring, protocols for patients at risk of diphenhydramine abuse, management of adverse events, and potential alternative and adjunctive therapies. In the meantime, patients requiring chronic parenteral diphenhydramine should be maintained at the lowest possible dose, and the selection of method of administration should include considerations of abuse potential. Pharmacists and patient providers should work collaboratively to optimize treatment regimens in these patients to prevent the misuse or abuse of diphenhydramine.

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