Title

First-generation Antipsychotics Are Often Prescribed in the Emergency Department but Are Often Not Administered with Adjunctive Medications

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FIRST-GENERATION ANTIPSYCHOTICS ARE OFTEN PRESCRIBED IN THE EMERGENCY DEPARTMENT BUT ARE OFTEN NOT ADMINISTERED WITH ADJUNCTIVE MEDICATIONS

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□ **Abstract—Background: Although first-generation antipsychotics (FGAs) have long been used in the emergency department (ED) to treat acute agitation, little is known about how these medications are used in modern clinical practice. In particular, little work has been published about whether ED clinicians administer FGAs with adjunctive medications in accordance with expert guidelines or the prescribing practices of FGAs over time. Objectives: 1) To provide a comparison of the frequency with which FGAs are administered with adjunctive benzodiazepines or anticholinergic medications. 2) To analyze the prescribing trends for FGAs over time, particularly in the years after the U.S. Food and Drug Administration (FDA) black-box warning for droperidol. Methods: This is a structured review of a retrospective cohort of patients receiving haloperidol or droperidol in two EDs over a 7-year period. Results: Haloperidol or droperidol was administered on 2833 patient visits during the study period, with haloperidol being administered most often. Adjunctive medications are administered less than half of the time. The use of droperidol has remained relatively static, whereas the use of haloperidol has increased. Conclusions: First-generation antipsychotics are still widely utilized in the ED. When administered, these medications are used with adjunctive medications that may decrease side effects less than half of the time. Droperidol use has remained unchanged in the years after the FDA black-box warning, whereas use of haloperidol has continued to rise.** © 2015 Elsevier Inc.

□ **Keywords—haloperidol; droperidol; first-generation antipsychotics; emergency department**

INTRODUCTION

Agitation can have life-threatening consequences for both patients and staff (1). Agitated patients are often treated with calming medications such as first-generation antipsychotics (FGAs) in the emergency department (ED) setting (2–5). The exact mechanism by which FGAs calm agitated patients is still an active area of research, but butyrophenones such as haloperidol and droperidol are potent antagonists at the D2 receptor (6,7). Although the D2 receptor, and in particular, the dopamine system, is not the only neurotransmitter implicated in psychosis, interruption of dopamine transmission nonetheless relieves psychotic symptoms in agitated patients (8–11). Given this, FGAs such as haloperidol and droperidol have a long tradition of use in the ED, and may be safer than some second-generation antipsychotics in alcohol-positive patients (12–16).

Although butyrophenones have minimal effects on vital signs, they are not without side effects. In particular, FGAs are known to cause both cardiac-related side effects and movement-related side effects such as tardive

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dyskinesia or dystonia (8,9,17–19). Given the black box warning by the U.S. Food and Drug Administration (FDA) issued in 2001, the safety profile of droperidol remains a controversial topic in ED literature, with several studies suggesting its safety in everyday clinical use (19–25). Although haloperidol has not received a black-box warning from the FDA, the risk of motor-related side effects is quite common in practice. A 2012 Cochrane review suggested that approximately 1 in 5 patients administered haloperidol developed some sort of acute dystonia (number needed to harm, 5; 95% confidence interval 3–9), and suggested that it was "somewhat surprising" that this medication continued to be used so widely as a comparison for new medication (18). Another Cochrane review suggested that the relative risk of dystonia with haloperidol alone may be more than that of droperidol alone, although these side effects can be reduced by using adjunctive medications such as benzodiazepines or medications with anticholinergic activity (26). In perhaps the largest ED-based study of its kind, Battaglia and colleagues (1997) examined the use of haloperidol with lorazepam in agitated patients (27). This study concluded that calming was more rapid and the incidence of motor-related side effects decreased in patients who received lorazepam in combination with haloperidol compared to haloperidol alone. A similar study involving haloperidol administered with promethazine concluded that this combination was more effective, with fewer side effects than a second-generation antipsychotic like olanzapine (28,29).

Although later reviews have disputed whether benzodiazepines such as lorazepam offset the movement-related side effects of FGAs, older consensus guidelines as well as current expert recommendations such as the recent American Association for Emergency Psychiatry Best Evidence in the Treatment of Agitation project continue to suggest adjunctive medication (9,30,31). The best evidence for adjunctive medications, studied in the TREC trials, is for promethazine in conjunction with haloperidol (28,29,35). Extrapyramidal side effects in patients receiving droperidol are usually treated in a similar manner, often with an anticholinergic medication such as diphenhydramine or promethazine (32). Little, however, is known about prescribing trends of droperidol or how its use compares to haloperidol in recent years. Little is also known about how often emergency clinicians prescribe adjunctive medication in accordance with expert consensus guidelines.

The primary objective of this study was to investigate the use of FGAs in the ED setting, particularly how often emergency clinicians administer FGAs with recommended adjunctive medications. We further hypothesized that alcohol-positive patients would receive adjunctive medication less often than alcohol-negative patients. The secondary objective of this study was if the use of droperidol has decreased over time due to FDA safety regulations. We hypothesized that patients would receive concomitant medications frequently with haloperidol in accordance with expert guidelines and that the use of droperidol has decreased over the study period.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective cohort study of patients who received haloperidol or droperidol in the ED of two hospitals between October 8, 2004 and December 30, 2011. This period was selected to evaluate whether FDA safety regulations had a lasting effect on the use of droperidol in the emergency setting. One hospital is an academic teaching hospital and the other is a community hospital with a combined census of approximately 65,000 visits per year.

Selection of Participants

The cohort included patients that received any of the following medications: haloperidol, haloperidol lactate, droperidol, Haldol® (Janssen Pharmaceuticals, Titusville, NJ), or Inapsine® (Akorn, Inc., Somerset, NJ) during their ED visit. Exclusion criteria included irretrievable charts, patients in which the medication was ordered but not received, or patients who presented with the chief complaint of medication refill. The local Institutional Review Board approved this study prior to data collection.

Data Collection and Processing

Patient visits were identified using keywords to query the electronic medical record (Webcharts®; Fort Wayne, IN). In the case of this study, the following variables were queried: age; gender; date of presentation; chief complaint; type of FGA given; and the route of administration. The only inclusion criteria was having received either haloperidol or droperidol.

At least two trained research associates blinded to research hypotheses then verified the electronically abstracted variables while manually abstracting the following information: use of adjunctive benzodiazepines (defined as lorazepam, midazolam, diazepam, or alprazolam, or their appropriate trade names) or other medication with anticholinergic properties (specifically, promethazine, benztropine, or diphenhydramine, or their appropriate trade names); and documented breathalyzer or serum alcohol levels. Adjunctive medication was defined as medication given within 30 min of the FGA. Alcohol-positive was defined as a positive breathalyzer performed

by ALCO-Sensor III® (Intoximeters Inc., St. Louis, MO) or by a positive quantitative serum test. Although a different modality of assessing blood alcohol levels, the Alco-Sensor III has been approved as an evidential testing device by the U.S. Department of Transportation, and per manufacturer specifications, is accurate to within .005 of the blood alcohol concentration (33).

After data abstraction, additional blinded research associates rechecked the entire data set for accuracy. In a second stage, the entire data set was then rechecked for inappropriate values by a senior investigator (MPW). In a third stage, 54 subjects were randomly selected using the Web site randomize.org for manual re-abstraction of key binary variables. The reliability of inclusion criteria was then subsequently calculated using Cohen's kappa. After other investigations using similar methodology, an agreement score of 0.6 was assumed to represent strong consensus (34).

Data Analysis

Descriptive statistics were utilized to analyze patient characteristics such as age, gender, rates of concomitant benzodiazepine use, and rates of anticholinergic medication use. Chi-squared analysis with Yate's correction was used to analyze categorical data such as differences between included and excluded patients, whether the frequency of adjunctive medication use was different between the FGAs of interest in this study, and to analyze the relationship between benzodiazepine use and alcohol use. The frequency of droperidol and haloperidol use over time was assessed using linear regression. In these analyses, time was broken into 29 separate 3-month periods. These time periods were utilized to determine if time significantly predicted the number of patient visits on which an FGA was administered; in other words, if use was significantly increasing over time. Descriptive statistics were performed using Microsoft Excel v. 2010 and Microsoft Access v. 2010 (Microsoft Corporation, Redmond WA). Regression analysis was performed using Systat 13 (Systat Software, San Jose, CA). Cohen's Kappa was calculated using GraphPad Prism (GraphPad Software INC., La Jolla, CA).

RESULTS

A total of 3157 visits were identified by simple query. Please see Table 1 for a list of excluded visits. Prior to data analysis, manual reabstraction was performed on inclusion criteria of a randomly selected group of cases. Cohen's kappa was calculated as 0.78, indicating strong consensus.

During the study period, FGAs were administered in 2833 patient visits to 2470 unique patients (mean age 43 ± 17 years, 49% female), with all statistics below analyzed by patient visit. The top chief complaints reported were head pain, 564 (19.9%); psychiatric evaluation, 404 (14.3%); altered level of consciousness, 312 (11.0%); abdominal pain, 199 (7.0%); and other, 1116 (39.4%). There was no difference in gender between included and excluded patients ($p = 0.33$). Haloperidol was used in 1470 (51.9%; mean age 46 ± 19 years, 35.1% female) of the visits at an average dose of 4.9 ± 4.5 mg, with intravenous administration being the most utilized route (47.0%). Oral administration was the least utilized route (6.3%). Droperidol was administered in 1363 patient visits (48.1%; mean age 39 ± 14 years; 64% female) at an average dose of 1.6 mg ± 1.4 mg, with the most common route of administration being intravenously (84.9%).

Table 1. List of Excluded Patient Visits

Reason for Exclusion	n
Did not meet inclusion criteria (i.e., not within study dates)	14
Chief complaint of medication refill	42
Medication ordered but not given	245
Medication apparently given for reasons other than agitation	15
Other (i.e., charting errors)	8

An adjunctive medication or combination of medications was used with either haloperidol or droperidol in 49.5% of the visits overall. A concomitant benzodiazepine was administered during 928 (32.4%) of the patient visits and was more frequent with haloperidol (53.5%) than with droperidol (10.1%; $p < 0.001$), with lorazepam being the most common benzodiazepine. A medication with anticholinergic properties was administered in 551 visits (19.4%), with diphenhydramine being the most common. Concomitant anticholinergic administration occurred significantly more often with droperidol (33.9%) than with haloperidol (5.9%; $p < 0.001$). The use of both adjunctive benzodiazepine and anticholinergic medication (colloquially known as a B52, indicating Benadryl, haloperidol, and lorazepam) was the least frequent in that it was administered in only 77 patient visits (2.7%).

Alcohol use was confirmed via serum or breathalyzer test in 468 patient visits (16.5%), with an average of 222 ± 106 mg/dL. Haloperidol was administered on 353 patient visits (75.4%) involving alcohol, whereas droperidol was administered on 115 visits (24.6%). During 236 (50.4%) alcohol-positive visits, a concomitant benzodiazepine was administered, compared to 24.4% (n = 692) of alcohol-negative patient visits ($p < 0.001$).

Medications differed in their frequency of use over the study period. Linear regression revealed that there was no change in droperidol use over the study period ($\beta = .046$,

$p = 0.92$). Haloperidol use, however, did significantly increase over time ($\beta = .616$, $p = 0.016$).

DISCUSSION

Although first-generation antipsychotics are a familiar medication class to emergency physicians, little is known about their actual use in the ED. The major findings of this study are that first-generation antipsychotics like haloperidol or droperidol are administered with adjunctive medications such as benzodiazepines, promethazine, benztropine, or diphenhydramine only 49.5% of the time. Although this study was not designed to investigate the beneficial effects of these combinations, it is notable that there is substantial literature that suggests the idea of doing so, specifically in the case of acute psychosis or undifferentiated agitation (9,28–31). In contrast to a 2012 Cochrane review, which suggested that 1 in 5 patients developed acute dystonia after administration of haloperidol alone, a second Cochrane review summarizing trials with haloperidol administered with promethazine found that approximately 1 in 15 patients developed some sort of preventable adverse effect after haloperidol alone (18,28). This review noted that "haloperidol used on its own is at such risk of generating preventable adverse effects that unless it is the only choice, this evidence directs that this sole treatment should be avoided" [(28), p. 2].

Despite the existing literature, clinicians in this study followed this guideline less than half of the time for unclear reasons. This finding may suggest that practice guidelines either do not accurately capture real-world best practices or that antipsychotics are often administered to patients without psychosis. Alcohol use does not explain the failure to administer concomitant medication, as a higher percentage of alcohol-positive patients were administered benzodiazepines than alcohol-negative patients.

There was no significant change in the prescribing rate of droperidol during the study period, which contradicts our initial hypothesis of overall decreased use in the years after the FDA black-box warning. However, given the decreased use relative to haloperidol, this may reflect relatively fixed prescribing patterns by some clinicians. Of note, although the frequency of droperidol use remained static, the frequency of haloperidol use increased significantly over the study period. The use of second-generation antipsychotics as a class has been decreasing in a statistically nonsignificant fashion during this exact period (5).

Limitations

There are some important limitations to this study. First, the investigators relied on a retrospective cohort of patients, in which abstraction of information relies upon contemporaneous charting by medical professionals. Thus, some variables of interest such as level of agitation could not be properly assessed and therefore were not included in the analysis. Other alcohol-positive patients may not have been included if a breathalyzer or serum alcohol level were not obtained, a form of misclassification bias. Due to the retrospective nature of this study, it is further limited in offering any concrete conclusions about when to use an FGA or FGA combination therapy because emergency clinicians may often administer these medications for reasons other than psychosis. Finally, the conclusions of this study are unique to the setting from which the data were collected. Although there is no reason to believe that the practice at these two EDs varies widely from other U.S. EDs, the uniqueness of any ED clinical practice is founded in the populations served, the hospital setting, and any hospital-wide protocols. In an ideal design, data would be collected from a number of sites across the nation in a number of settings. Nonetheless, the sample size in this study should still be sufficient to offer a description of general FGA prescribing trends in an emergency setting.

CONCLUSIONS

Despite expert guidelines that recommend second-generation antipsychotics, the use of haloperidol is increasing over time. When given, FGAs are often not administered with adjunctive medications, as recommended in existing literature. Further study is needed to examine these trends nationwide and to investigate reasons for the departure by emergency clinicians from expert guidelines.

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ARTICLE SUMMARY

1. Why is this topic important?

First-generation antipsychotics (FGAs) such as haloperidol and droperidol are frequent treatments for acute agitation in the emergency department. Despite their long history of use, their actual prescribing trends are unknown, in particular, the frequency with which they are used with recommended adjunctive medications to decrease the incidence of side effects; how often FGAs are used in patients with alcohol; or how the FDA black-box warning has affected the prescribing of droperidol.

2. What does this study attempt to show?

This study attempts to show that despite recommendations for the use of adjunctive medications with FGAs to decrease side effects, adjunctive medications are administered <50% of the time. In addition, the use of haloperidol has been increasing over time, whereas the use of droperidol has remained relatively static.

3. What are the key findings?

In this study, adjunctive benzodiazepines or anticholinergic medications are administered with first-generation antipsychotics less than half the time. Droperidol use has been relatively static in the years since the U.S. Food and Drug Administration black-box warning, but haloperidol use has been increasing.

4. How is patient care impacted?

The reason why adjunctive medications are not administered frequently with FGAs is unclear, but it does not seem to involve alcohol. Use of FGAs without adjunctive medications may increase the incidence of side effects. This practice has been challenged by best practices guidelines, and reasons for the departure from best practice guidelines by emergency clinicians should be evaluated further.