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Harms From Haloperidol for Symptom Management in Palliative Care—a Post Hoc Pooled Analysis of Three Randomized Controlled Studies and Two Consecutive Cohort Studies



Introduction

Symptom control for people with cancer improves quality of life. Haloperidol is a key drug in palliative care and is frequently used for the treatment of delirium, nausea, and vomiting.¹ Haloperidol, a butyrophenone, is a more potent D₂ receptor antagonist than other antiemetics, such as prochlorperazine, olanzapine, or chlorpromazine.

The adverse events associated with haloperidol are like those of the phenothiazines, except that haloperidol potentially causes less sedation and hypotension. However, haloperidol is more strongly associated with extrapyramidal symptoms especially compared with newer drugs such as quetiapine or risperidone, and patients with Parkinson disease or Lewy body dementia may be more sensitive to its adverse events.² Haloperidol is inexpensive and has several routes of administration. Only a few studies focus on patients with life-limiting illnesses. The aim of this study was to determine whether the doses of haloperidol used in palliative care cause immediate and short-term harms and, if so, what is their severity?

Material and Methods

This study was a *post hoc* analysis conducted on three randomized controlled trials (studies 1, 2 [nausea], and 3 [delirium])^{3–5} and two international

collaborative Phase IV consecutive cohort studies (studies 4 [nausea] and 5 [delirium]),^{6,7} which have been described previously. Severity of immediate and short-term harms were assessed using the National Institutes of Health Common Terminology Criteria for Adverse Events.^{8,9} Nausea was graded by clinicians using verbal descriptors (none, mild, moderate, or severe). Items and evaluation times for harms differed between studies. Most frequently, routine data were collected at baseline and days 1, 2, and 7.

This study reports the number and percentage of participants with severity ≥ 3 grade and symptom deterioration ≥ 1 point from baseline in symptoms of interest. Harms in all five studies could also be reported on an *ad hoc* basis.

Descriptive statistics are used in this study, with categorical variables summarized as frequency and percentages, and continuous variables with median and interquartile ranges (IQRs).

This study is generated from secondary use of deidentified data that have been aggregated. All participants in studies 1–3 gave written informed consent, and the studies were approved by the relevant Human Research Ethics Committees before recruitment commenced. For studies 4 and 5, these were capturing routine data after the clinician had made the decision to commence haloperidol for the indication being studied. Sites had waivers of consent for collection of these deidentified clinical data and ethics approvals or waivers depending on the country in which the data were collected to publish the analyses.

Results

Patients' Characteristics

The clinical and demographic data of the 494 subjects are shown in [Table 1](#). In the present study, the most subjects (90%) had advanced metastatic cancer (94% in studies 1–3 [Phase III] and 87% in Phase IV studies, respectively). The median age was 73 years (IQR: 64.5–81), and median Australia-modified Karnofsky Performance Scale score¹⁰ was 40 (IQR: 30–50), indicating that many subjects required “considerable assistance and frequent medical care.” AKPS in Phase III studies was better than the Phase IV studies. The median daily dose of haloperidol was 1.5 mg (day 1), 2.0 mg (day 2), 1.5 mg (day 7) in oral, or parenterally preparations.

Harms

Potential harms from treatment with haloperidol and the clinical responses to address those symptoms are shown in [Table 1](#). Harm in this study was defined as a one-point deterioration from baseline in the National Institutes of Health Common Terminology Criteria for Adverse Events for the relevant symptom.

Table 1

Comparison of the Characteristics of Participants in Phase III Clinical Studies for Symptom Control ($n = 226$) With the Phase IV Palliative Care Populations ($n = 268$)

Item	Phase IV Pharmacovigilance	
	Population ($n = 268$)	Phase III ($n = 226$)
Age, Median (IQR)	73.0 (65-81)	73.0 (64-80)
Sex, n (%)		
Men	130 (48.5)	95 (42.0)
Women	137 (51.1)	127 (56.2)
Missing	1 (0.4)	4 (1.8)
Diagnosis, n (%)		
Cancer	234 (87)	211 (94)
End-stage disease (cardiac, renal, hepatic, respiratory)	14 (5)	2 (1)
Neurodegenerative disease	3 (1)	3 (1)
Other	17 (7)	10 (4)
AKPS, median (IQR)	40 (30–50)	50 (40–60)
Symptom control		
Nausea and/or vomiting	150	145
Delirium	118	81
Treatment emergent adverse events \geq grade 3 cumulatively by day 7		
Anorexia	0	0
Constipation	1 (1.0)	0
Dizziness	0	1 (0.8)
Hypertension	0	0
Rigidity	0	0
Somnolence	0	12 (5.6)
Dry mouth	1 (1.0)	0
Extrapyramidal reaction	0	0
Diarrhea	0	0
Hypotension	0	0

Frequently reported harms were somnolence (1.9, 2.0, and 2.9% on day 1, 2, and 7, respectively), and treatment emergent harms \geq grade 3 cumulatively by day 7 were seen in 5.6% patients in Phase III studies. In terms of rigidity including extrapyramidal symptoms, there were no reports of any events graded ≥ 3 . Even when including harms graded 1 or 2, one event was reported on each of days 1, 2, and 7.

Discussion

To our knowledge, this study is the first study to evaluate the harms of haloperidol in palliative care. This study was a *post hoc* analysis conducted on three adequately powered, randomized, controlled trials, and two consecutive cohort studies where all data were collected prospectively searching for specific adverse events from haloperidol that had previously been identified in the literature.

The study is limited to the immediate and short-term harms from the introduction of haloperidol, but the most remarkable thing is how well the medication is tolerated. Other harms or worsening of emerging adverse events will occur over time, and further research is required to elucidate these clinical effects. The doses used tend to be lower (≤ 2 mg/day)

than many reports in the literature from contemporary practice.

Taking these limitations into consideration, we believe our results support the use of low-dose haloperidol in palliative care settings for nausea and vomiting (given the study in delirium was strongly negative and consistent with the findings of several systematic reviews).

In conclusion, low-dose haloperidol was tolerated well in the immediate and short term in a frail population of people mostly with advanced cancer. Further work should be carried out to follow a similar cohort of patients for a longer period of time with prospective bespoke data collection to map the emergence of any mid- and long-term harms.

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Candidate Claims-Based Indicators of Functional Impairment: An Exploration in a Sample of Medicare Beneficiaries



Introduction

Recent healthcare reforms aim to improve the quality and reduce the costs of care for seriously ill adults.¹ Palliative care and other programs focused on care for seriously ill adults typically rely on provider referrals to identify patients, an approach which may lack sensitivity (i.e., may miss those who could benefit) and specificity (i.e., may refer patients with low needs). Systematic case-finding using data from the electronic health record and administrative claims could improve on provider referral in terms of finding all (and only) those with palliative care needs. Such a targeted approach would help to maximize the potentially beneficial impact of a high resource clinical intervention and facilitate value-based care.

In 2018, an expert advisory committee to the Department of Health and Human Services recommended the agency test two alternative payment models for the delivery of community palliative care. In both models, functional impairment is an eligibility criterion for the receipt of palliative care.^{2,3} However, functional status is not captured consistently across providers or settings limiting its application within systematic case-finding approaches. We therefore sought to test whether a claim for selected