The Effect of Butyrophenones for the Management of Primary Headache in the Emergency Department: A Systematic Review and Meta-Analysis

Ahmed Alsuliamani, Rizq Badawi, Erich Hanel, and Sharafaldeen Bin Nafisah

Abstract—**BACKGROUND: The use of butyrophenones for headaches became plausible when the association was established between dopamine and headache. However, despite their positive effect on acute headaches, their use remains controversial.**

AIM: The goal of this study is to ascertain whether the addition of haloperidol or droperidol to the treatment regimen for acute primary headache lowers the pain score of adult patients in the emergency department.

METHODS: A systematic review and meta-analysis was conducted. We searched the following databases for randomised controlled trials (RCTs): PubMed, Cochrane databases, and grey literature, from 1963 to October 2022. Included were RCTs conducted on the use of butyrophenones (IV haloperidol or IV/IM droperidol) in the acute management of primary headaches (diagnosed or undiagnosed), designated prospective, double-blind or open, using only the Visual Analogue Scale (VAS) with a specific measurement time. We excluded non-English studies that lacked translation, studies conducted on paediatric age groups, and studies conducted on animals.

RESULTS: Out of 49 articles we included seven, three of which investigated haloperidol. The mean difference in VAS score favoured haloperidol; -2.46 (95% CI: [-4.11 to -0.81]), indicating a drop in VAS score of 2.5/10 units. The mean difference in VAS score for the use of droperidol was -0.35 (95% CI: [-1.24 to 0.54]).

CONCLUSION: Haloperidol can induce an acute 25% reduction in VAS score when added to the regimen for acute headache management. It also reduces the need for rescue medications and improves patient satisfaction. Nonetheless, considerable side effects cannot be overlooked.

***Index Terms*—Butyrophenones, Droperidol, Haloperidol, Headache Disorders**

I. INTRODUCTION

Headache is a commonly-managed symptom in the emergency department (ED) setting. One study reported that, in one year, more than three million patients presented to the ED complaining of headache, making this a common chief complaint [1]. Nonetheless, the diagnosis and management of primary headache disorders receive inadequate attention and the undertreatment of such patients is prevalent [2,3]. This can be attributed to the fact that the management approach of ED physicians is tailored toward life-threatening causes of headaches, including but not limited to meningitis, subarachnoid haemorrhage (SAH), and intracranial mass.

The high burden of primary headaches is not limited merely to their prevalence [4]. The sequelae of absenteeism and reduced productivity also carry economic costs [5,6]. Lower satisfaction with ED management, and with health care in general, is another important but often-overlooked factor that results from undertreatment. Conversely, the earlier and the more successfully a patient's headache is addressed, the higher their satisfaction rate [7].

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The literature on the acute treatment of primary headache disorders is extensive, spanning decades. The use of butyrophenones for headaches became plausible when the association was established between dopamine and headache [8]: these medications' action as a dopamine receptor antagonist made them a treatment of choice for such disorders. However, despite their positive effect in several randomised controlled trials, their use remains discouraged given the low level of evidence and the concern regarding their side effects [9].

The incidence of side effects from the use of butyrophenones was as high as 45% [10]. Those side effects include akathisia, anxiety, prolonged QT interval, and sedation. The resulting risk of torsade de pointes and sudden death was reported in several analyses [11, 12]. However, further knowledge of the medications' delivery routes and the underlying risk factors might influence our understanding of the cause-and-effect relationships involved [13-15].

A previous systematic review attempted to explore the effect of butyrophenones on primary headaches [10]; it concluded that these medications are effective, yet their side effects should not be disregarded. Nevertheless, the small number of included articles, the combination of haloperidol with droperidol, as well as the different outcome measures, might have exaggerated the positive findings. Hence, despite the performance of several randomised controlled trials (RCTs), the literature still lacks a solid conclusion as to whether butyrophenones should be advocated for acute primary headache.

Thus, in this review, we aim to investigate the efficacy of butyrophenones (haloperidol and droperidol) for the acute management of primary headache in the ED. We also aim to explore their effect on patients' return to the ED, their side effects, and patients' reported satisfaction rates.

II. METHODS

Research question:

Does the addition of butyrophenones (haloperidol or droperidol) to the treatment regimen for acute primary headache reduce the pain score of adult patients in the emergency department?

Search strategy:

We searched the following databases: PubMed, Cochrane databases, and grey literature (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform). We also searched the reference lists of included articles.

Search method MeSH terms was:

Exp headache, 2 exp migraine, 3 exp haloperidol, 4 exp droperidol, 5 exp butyrophenones, 6 exp 1 and 3, 7 exp 2 and 3, 8 exp 1 and 4, 9 exp 2 and 4, 10 exp 1 and 5, 11 exp 2 and 5.

The search aimed to identify randomised controlled trials comparing butyrophenones (haloperidol or droperidol) with placebo or an active control in adult patients with acute headaches. This search strategy yielded 49 articles, of which 33 were excluded because they were review articles, 3 were excluded because they were systematic reviews, 1 described national practice patterns for headache treatment, 1 was a letter or case report, 1 was non-English, and 1 was retrospective. The remaining 9 articles were retained and reviewed, and 2 of those were excluded: the first due to use of haloperidol at a different dose in the control group, and the second because it did not use the VAS score to measure the outcome. The 7 included articles are summarised in Table 1 and Table 2.

Selection criteria:

The inclusion criteria were all RCTs conducted on the use of butyrophenones (haloperidol and droperidol) in the acute management of primary headaches (diagnosed or undiagnosed), designated prospective, double-blind or open, using only the Visual Analogue Scale (VAS) with a specific measurement time. We excluded non-English studies that lacked translation, studies conducted on paediatric age groups, and studies conducted on animals. We also excluded articles that did not use the Visual Analogue Scale (VAS) to measure the intensity of headache pain.

Data extraction, quality assessment, and qualitative synthesis:

The studies' eligibility for inclusion in our review was examined by the first two authors independently; another researcher was consulted in the event of any disagreement regarding a study's inclusion. As illustrated in Table 3, we applied the RoB 2, a revised Cochrane risk-of- bias tool for randomised controlled trials, to assess the bias of the included studies [16].

Data analysis:

Continuous variables were used and a mean difference was calculated. The data were analysed using the mean difference in pain score between pre- and post-administration of the medications. We used the maximum (or longest) reported patient observation period. Review Manager Web was used to perform the meta-analysis, employing a random-effects model on the assumption that the true effect size would vary from one study to another [17]. We used the I^2 statistic to assess for heterogeneity. In the event that data was missing from any included study, we planned to contact the authors before applying a mean imputation strategy according to the Cochrane guidelines for imputing missing data [18]. This review was written in accordance with the Preferred Reporting Items for a Review and Meta-analysis of Individual Participant Data [19], and was approved by the IRB committee with log number 22-579.

Outcomes:

The primary outcome was the difference in VAS score after administering butyrophenones (haloperidol or droperidol) for patients visiting the ED with primary headaches. The secondary outcome was the effect of butyrophenones on the need for rescue medication, patients' return to ED, patient satisfaction, and side effects.

III. RESULTS

Study selection:

Out of 49 articles we included seven, three of which investigated haloperidol, as illustrated in the Prisma chart (Figure 1). Two studies [20, 21] were excluded: the first used haloperidol in the control group with a different dose, and the second did not use the VAS score to measure the outcome. The included articles are illustrated in Tables 1 and 2. We calculated the standard deviation (SD) from the 95% confidence interval using the formula:

SD= N * (upper limit-lower limit)/3.92

We attempted to contact the authors of one of the included studies to retrieve the SD [22], but failed to receive an answer; we therefore imputed the missing SD. Table 4 illustrates the risk of bias in the included articles.

Demographic characteristics:

A total of 608 patients were included in this analysis, of which 198 (32.6%) were male and 410 (67.4%) female. The mean age of the patients was 32.4 years. All of the haloperidol studies excluded patients with a prolonged QT interval at baseline, while patients with possible secondary headache were excluded from all of the studies.

Efficacy of IV haloperidol:

The total number of patients in the haloperidol analysis was 222, of whom 109 received intravenous haloperidol and 113 were in the control group. The mean VAS score in the treatment group was 7.6 (SD 0.91) at baseline, and in the control group 7.4 (SD 0.89).

The mean difference between pre- and post-medication VAS scores in those receiving haloperidol was 5.29 (SD 0.47), compared with 2.56 (SD 2.09) in the control group.

The pooled effect size or mean difference in VAS score favoured haloperidol; -2.46 (95% CI: [-4.11 to -0.81]). The total effect size indicates a drop in VAS score of 2.5 units out of 10, or 25 mm of the 100 mm scale. However, significant substantial heterogeneity was noted; the forest plot is illustrated in Figure 2. A funnel plot revealed no evidence of publication bias, as illustrated in Figure 3.

Need for rescue medication after administering haloperidol:

The use of haloperidol significantly reduced the need for rescue medication by 35% (p=0.002), as illustrated in Figure 4. However, one study [24] was omitted from this analysis as haloperidol was used as a rescue medication, and it was unclear whether any other drug was used thereafter.

Return to ED and patient satisfaction:

Of the included patients who received haloperidol, 6.42% (n=7) returned to the ED after discharge, whereas 11.5% (n=13) returned from the control group. The rate of satisfaction after receiving haloperidol was 72% (n=79).

Side effects:

Nausea and vomiting were excluded from our analysis given the variation in the control groups, as well as the fact that those are symptoms of several primary headache disorders. Akathisia, agitation and anxiety were reported in 32 patients who received

Table 1. Summary of included studies assessing droperidol

Reference	Study Design	Patients	Efficacy End Points	Safety End Points
Miner et al. [27]	• P, SB (patient only) • Convenience sample of patients presenting with benign HA • Randomized to droperidol (5 mg IM or 2.5 mg IV) versus prochlorperazine (10 mg IM or 10 mg IV) based on physician preference	n = 168: droperidol (n = 82), prochlorperazine (n = 86) Baseline results • Average age 31.7 years versus 33.9 years • 50% Female in both groups (NS) • Baseline pain scores, assessed with a 100 mm VAS (0 = no pain, 100 = most severe pain) were similar in both groups (79.8 mm versus 74.3 mm, P = 0.08). • IM was administered to 59.8% versus 66.3%, P = 0.12. • Medication use prior to treatment in ED was similar between groups: 34/82 (41.5%) versus 29/86 (33.7%), P = NS. Most commonly used medication class was NSAIDS	Results • At 60 minutes, mean change in VAS score from baseline; 81.4% (95% CI = 76.1-86.8) versus 66.9% (95% CI = 59.9-73.9), P = 0.007. • At 60 minutes, 50% change in VAS score; 90.2% versus 68.6%, P = 0.017. • Rescue medication administration was similar in both groups • Rebound HA incidence was similar at 24 hours; 26% versus 18.2%, P = 0.36	Results Side effects occurred more often in those receiving droperidol; 15.2% versus 9.6%, P = 0.19. Droperidol side effects • Decreased level of consciousness, 8.5% • Akathisia, 6.1% • Dystonia, 1.2% Prochlorperazine side effects • Akathisia, 8.1% • Decreased level of consciousness, 1.2% • No reports of arrhythmias or hypotension were reported
Weaver et al. [28]	• P, RCT, DB • Adult patients with an uncomplicated HA (normal neurological examination) • Droperidol 2.5 mg IV versus prochlorperazine 10 mg IV • Rescue medications (meperidine, ondansetron, or diphenhydramine) given for persistent HA, N/V, or EPS	n = 96; droperidol (n = 48), prochlorperazine (n = 48) Baseline results • Median age: 30 years versus 34 years, P = 0.27. • Female gender: 91.7% versus 81.3%, P = 0.14. • Baseline pain scores, assessed with a 100-mm VAS were similar between groups: 68 versus 79 mm, P = 0.07	Results • At 30 minutes, 83.3% versus 72.3% achieved a 50% reduction in HA intensity (95% CI = −2.9% to 100%) • At 30 minutes, 54.2% versus 38.3% who achieved 100% pain relief (95% CI = −0.7% to 100%) • Mean decrease in HA intensity at 30 minutes was 79.1% versus 72.1%, P = 0.23 • Six patients in each arm required rescue treatment for HA pain with meperidine • At 24 hours, similar rates of HA were reported in both groups (27.5% vs 34.8%, P = 0.47) and similar proportions returned to normal daily activities (67.5% vs 65.1%, P = 0.82)	Results • Rates of akathisia within the first 60 minutes were similar between groups: 10.5% versus 18.8%, P = 0.25 • No other adverse effects were reported
Richman et al. [22]	• P, RCT, DB • Convenience sample of patients meeting IHS criteria for migraine with or without aura • Droperidol 2.5 mg IM or meperidine 1.5 mg/kg IM • Patients excluded if they used any of the following within 24 hours of presentation: antiemetic, antihistamine, phenothiazine, or narcotic	n = 29: droperidol (n = 15), meperidine (n = 14) Baseline results • Average age: 30.7 years versus 32.7 years • Gender: 73% female versus 71% female • HA duration at baseline: 24.7 hours versus 18.3 hours • Baseline pain scores assessed with a 100-mm VAS were higher in the droperidol group (88 vs 76 mm, P = 0.03)	Results • VAS change at 30 minutes: 47 versus 37 mm, P = 0.33 • Patients who felt good enough to go home at 30 minutes: 67% versus 57%, P = 0.61	Droperidol side effects • Sedation, 6.7% • Akathisia, 13.3% Meperidine side effects • Sedation, 14.3%
Hill et al. [26]	• P, RCT, SB (patient) • Convenience sample of adult patients presenting to the ED with a suspected primary HA • Droperidol 5 mg IM versus olanzapine 10 mg IM	n = 87: droperidol (n = 42), olanzapine (n = 45) Baseline results • Average age: 34.6 years versus 32.5 years • Gender: 73.8% female versus 77.8% female • Baseline HA pain scores, assessed with a 100-mm VAS (83.9 vs 84.2 mm) • Median HA duration was 3 days in both groups • Migraine, 57.1% versus 66.7% • Tension HA, 21.8% versus 15.6%	Results • At 30 minutes, the scores were 42.7 versus 44 mm, P = 0.8, and the percentage decrease in pain was 52.2% versus 56.8%, P = 0.53 • At 60 minutes, the scores were 35.9 and 29.7 mm, P = 0.37, and the percentage decrease in pain was 58.7% versus 63.9%, P = 0.30 • No patient received a rescue medication within 60 minutes • After 60 minutes, 6/42 versus 4/45 received either droperidol, sumatriptan, morphine, olanzapine, or unspecified narcotic	Results • At 60 minutes, median AMS score was similar between groups (0, IQR = −1 to 0, versus 0, IQR −1 to 0, P = 0.83). • At 60 minutes, median BAS scores were similar between groups for each domain of the scale Awareness (0, IQR = 0 to 0, versus 0, IQR = 0 to 0, P = 0.82) Distress (0, IQR = 0 to 0, versus 0, IQR = 0 to 0, P = 0.44) Global (0, IQR = 0 to 0, versus 0, IQR = 0 to 0, P = 0.43) QTc at 30 minutes was 0.405 ± 0.052 s versus 0.377 ± 0.029

Abbreviations: AMS, altered mental status; BAS, Barnes Akathisia Scale; DB, double blind; DRS, dose-ranging study; ED, emergency department; EKG, electrocardiogram; EPS, extrapyramidal symptoms; HA, headache; IHS, International Headache Society; IM, intramuscular; IQR, interquartile range; IV, intravenous; MC, multicenter; N, nausea; NS, nonsignificant; NSAIDS, nonsteroidal antiinflammatory drugs; P, prospective; RCT, randomized controlled trial; SB, single blind; VAS, Visual Analog Scale; V, vomiting. No statistics were done on this metric and no baseline data were reported to know if there was a change.

Table 2. Summary of included studies assessing haloperidol

Reference	Study Design	Patients	Efficacy End Points	Safety End Points
Gaffigan et al. [23]	• P, RCT, DB • Inclusion criteria were diagnosis of migraine as defined by the criteria of the International Headache Society Classification Committee for migraine. • Randomised to haloperidol 5 mg IV versus metoclopramide 10 mg IV	n = 64: haloperidol (n = 31), metoclopramide (n = 33) Baseline results • Mean age 29 years versus 29 years • Female gender: 87% versus 76% • Baseline pain scores, assessed with a 100 mm VAS (0 = no pain, 100 = most severe pain), were similar in both groups. • The VAS pain scores for the haloperidol and metoclopramide groups did not differ at baseline, at the last recorded measurement, or in the magnitude of the pre-post treatment change ($p > 0.05$). • Average measurement interval in which the subjects' lowest VAS score was first recorded: 55 min for metoclopramide, 56 min for haloperidol ($p > 0.05$; VAS) • Medication use prior to treatment in ED was similar between groups: Diphenhydramine 25 mg IV, followed by the study medication.	Results • The mean reduction in pain from baseline to the last recorded measurement using the 100-mm VAS scale was statistically and clinically significant for both haloperidol- and metoclopramide-treated groups: 57 mm for the haloperidol group and 49 mm for those treated with metoclopramide ($p < 0.01$ for each comparison). • Eight of the 33 subjects in the metoclopramide group (24%) were given rescue medications, compared with only 1 of the 31 subjects (3%) receiving haloperidol ($p < 0.02$).	Results There were no differences in side effects while in the ED, with a tendency for more restlessness with haloperidol (NS, $p < 0.051$). Haloperidol side effects • Sleepiness 16% • Nausea 0% • Restlessness 32% • Chest pain 6% Metoclopramide side effects • Sleepiness 27% • Nausea 3% • Restlessness 12% • Chest pain 0% • Mean QTcs were equal and normal in the two groups and did not change after treatment for either group. • No dysrhythmias were reported. The four subjects reporting chest pain were re-evaluated and received repeat ECGs; subsequently, they were not deemed to require further cardiac evaluation.
Honkaniemi et al. [24]	• RCT, DB • Adult patients with an uncomplicated HA (normal neurological examination) • 5 mg haloperidol in 500 mL normal saline or 500 mL normal saline alone, as a 20 to 30 minute infusion • Rescue medications (meperidine, ondansetron, or diphenhydramine) given for persistent HA, N/V, or EPS	n = 40; haloperidol (n = 20), placebo (n = 20) Baseline results • Average age: 36 years • Female gender: 85% • Baseline pain scores, assessed with a 100-mm VAS: Before treatment, the mean VAS values did not differ significantly between the treatment groups (7.7 in the haloperidol group and 7.2 in the placebo group). • Almost all patients (43; 91%) had taken some kind of medication for their migraine attack prior to hospitalisation, without response: 27 (57%) had taken triptans, 24 (51%) NSAID-type analgesics, 13 (28%) paracetamol, 3 (6.4%) tramadol, 5 (11%) a combination preparation containing NSAID and codeine, and 3 (6.4%) metoclopramide. About half of the patients (23; 49%) had tried more than one type of medication before seeing a physician.	Results • Infusion of placebo or haloperidol caused a statistically significant reduction in headache intensity: the VAS values dropped to 6.3 after placebo ($P < .01$) and 2.3 after haloperidol ($P < .0001$). • The post-infusion values • were significantly lower in the haloperidol group ($P <$ • .0001). • Sixteen of the 20 patients (80%) who received haloperidol in the double blind trial felt marked relief from the pain, whereas only 3 of the 20 patients (15%) responded to placebo. This difference was statistically significant ($P < .0001$, chi-square test for independence).	Results The patients who received haloperidol in the double blind (16; 80%) or open (21; 88%) trial complained of side effects. Haloperidol side effects • Motor agitation: in DB 53%, in open 50% • Sedation: in DB 53%, in open 33% • Three patients treated with haloperidol (7%) returned to the emergency ward because of a repeat attack within 2 to 3 days after the infusion. • Symptomatic hypotension was not observed at all, although an electrocardiogram (EKG) was not performed on the patients prior to infusion. • There were no reports of arrhythmias or hypotension. • More severe extrapyramidal side effects were not observed among the haloperidol-treated patients in this study.
McCoy et al. [25]	• P, RCT, DB • Convenience sampling performed on patients aged 13 to 55 years presenting to the ED with a chief complaint of headache or migraine • 2.5 mg of IV haloperidol or placebo • Primary outcome measure was pain reduction at 60 min. • Patients were evaluated for adverse events and follow-up was conducted after discharge. QT measurement was performed at baseline and discharge.	n = 118: haloperidol (n = 58), placebo (n = 60) Baseline results • Median age: 31.5 (32.5 years versus 29.5 years • Female gender: 86% (37% versus 49%) • VAS was measured prior to treatment and at 60 minutes, for haloperidol and control groups, with and without rescue treatment, using means and SD. • Mean (SD) baseline VAS was 8.40 (1.50) and 8.35 (1.54) in the haloperidol and control groups, respectively.	Results • There was a statistically significant greater reduction in pain in the haloperidol group. • Patients in the haloperidol group reported an average 4.77-unit reduction in VAS score at 60 minutes compared with a 1.87-unit reduction in the control group. • Patients receiving haloperidol had a greater pain reduction from baseline at 30 and 60 minutes. Both of these time points for the haloperidol group were statistically significant ($p = 0.003$ and $p < 0.0001$). • The haloperidol reported a mean 4.77-unit reduction in VAS at 60 min compared with a 1.87-unit reduction in the control group. Thirty-four patients (58.6%) in the haloperidol group had complete resolution of their headache. Treatment with rescue ketorolac was required in 78.3% of the control group and 31% of the haloperidol group.	The most common adverse event was nausea/vomiting. Mean (SD) QT in the haloperidol group (366.16 [30.91] ms) was not statistically different from that of the control group (357.17 [37.83] ms). The mean change in QT at discharge (8.74 vs. 6.5) was also not statistically different or clinically significant. There were no observable dysrhythmias in either group. No patient complained of chest pain or palpitations, and no clinically significant increase in heart rate was observed.

Abbreviations: AMS, altered mental status; BAS, Barnes Akathisia Scale; DB, double blind; DRS, dose-ranging study; ED, emergency department; EKG, electrocardiogram; EPS, extrapyramidal symptoms; HA, headache; IHS, International Headache Society; IM, intramuscular; IQR, interquartile range; IV, intravenous; MC, multicenter; N, nausea; NS, non-significant; NSAIDs, non-steroidal anti-inflammatory drugs; P, prospective; RCT, randomised controlled trial; SB, single blind; VAS, Visual Analog Scale; V, vomiting. No statistics were done on this metric and no baseline data were reported to know if there was a change.

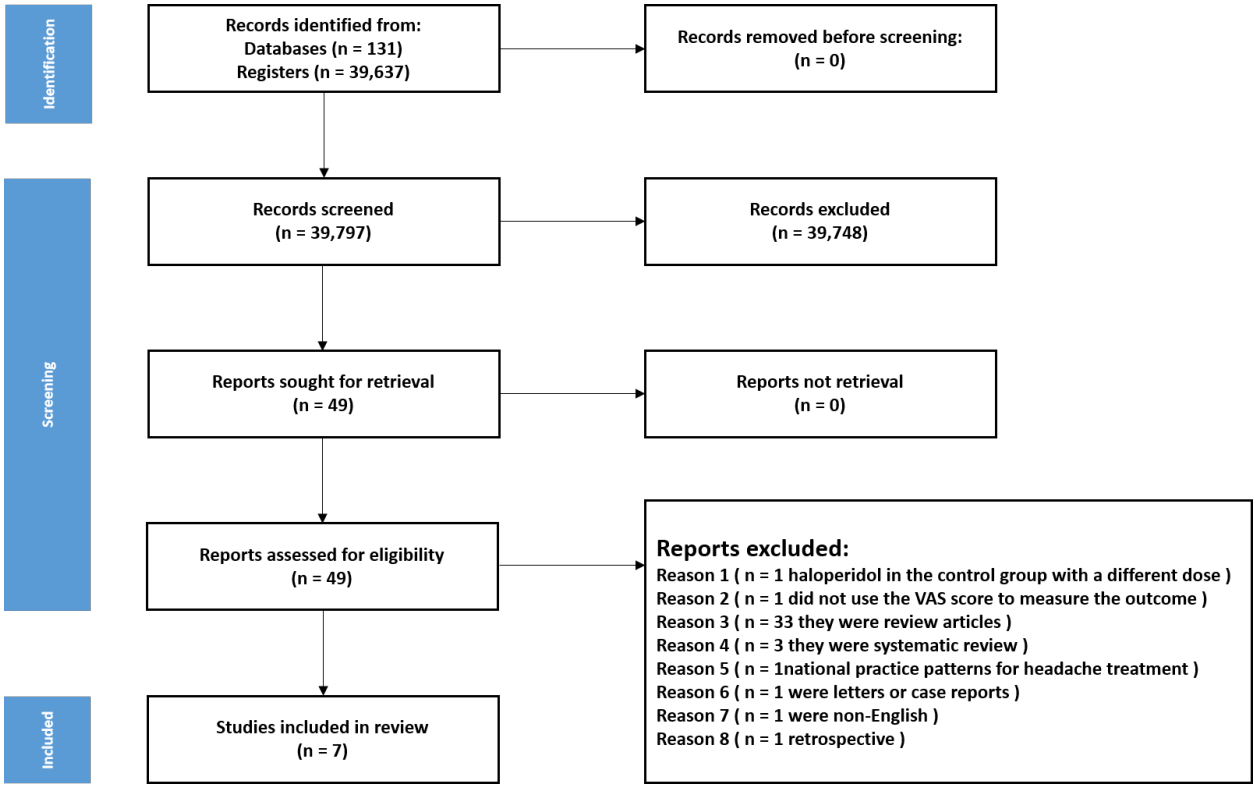

Figure 1. PRISMA chart

Table 3. Risk of bias in the included articles

	Inclusion	Sequence generation	Allocation concealment	Blinding of participants and trial personnel	Blinding of outcome data	Incomplete outcome data	Selective outcome reporting	Other sources of bias
1	McCoy et al. [25]	+	+	+	+	+	+	±
2	Honkaniemi et al. [24]	+	+	+	+	±	-	+
3	Gaffigan et al. [23]	+	+	+	±	+	+	+
4	Richman et al. [22]	+	+	-	-	+	-	+
5	Hill et al. [26]	-	-	-	+	+	+	+
6	Miner et al. [27]	-	-	-	+	+	+	+
7	Weaver et al. [28]	+	+	+	+	+	+	+

+ Yes/probably yes
- Probably No/No
± No information

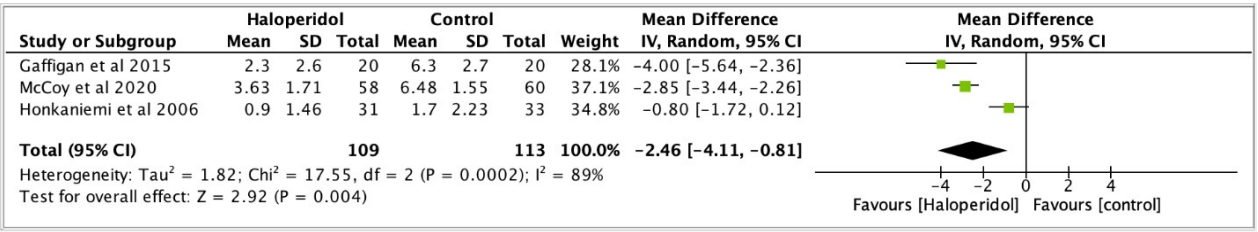

Figure 2. Forest plot of the effect of IV haloperidol in patients with primary headache

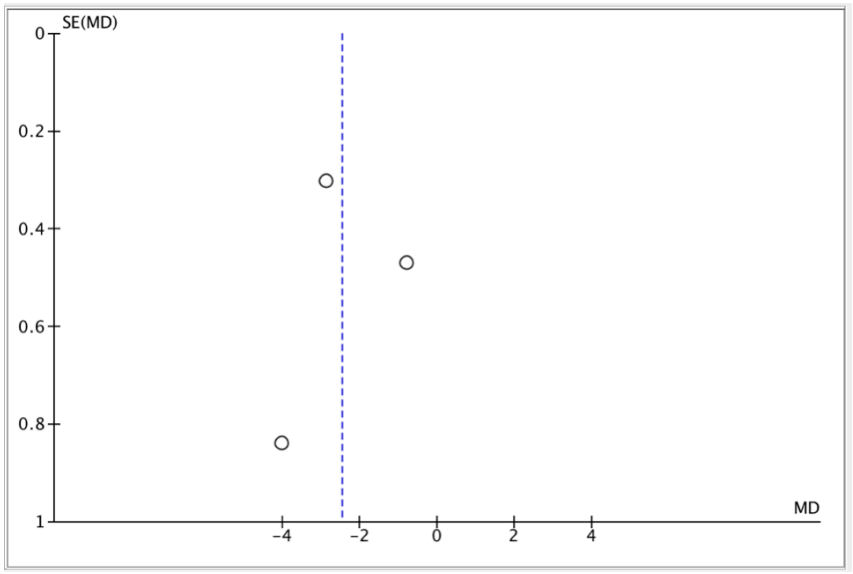

Figure 3. The funnel plot of the included studies reveals a symmetrical distribution

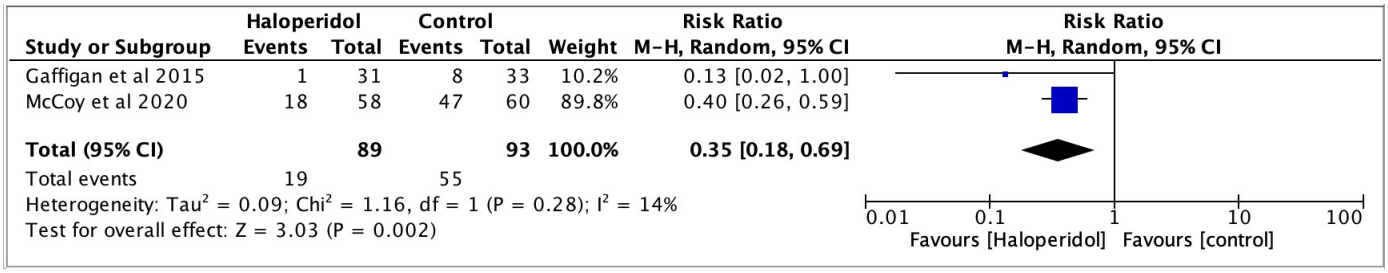

Figure 4. Forest plot of the need for rescue medication after IV haloperidol

haloperidol (29.4%), whereas sedation was reported in 14 patients from two studies, comprising 27.5%.

In two articles on haloperidol, McCoy et al. [23] and Gaffigan et al. [25] reported a change in the QT interval. The average change in the treatment group was 6.37 ms, whereas the average change in the control group was 9.25 ms. However, the latter study did not capture all of the patients' readings, and thus a firm judgement cannot be reached regarding such findings.

Quality assessment:

As per Table 3, an overall quality assessment revealed a low risk of bias, and therefore our findings from these articles can be generalisable. However, some information may be missing with regard to ECG changes and QTc prolongation or arrhythmias, which precludes our effort to further investigate the side effects.

Efficacy of IV/IM droperidol:

The total number of patients in the droperidol analysis was 380, of whom 187 received droperidol and 193 were in the control group. The mean VAS score for the treatment group was 7.99 (SD 1.89) at baseline, and 7.84 (SD 1.96) for the control group.

The mean difference between pre- and post-medication VAS scores in those receiving droperidol was 5.39 (SD 1.12), compared with 5.17 (SD 1.26) in the control group.

The pooled effect size or mean difference in VAS score was -0.35 (95% CI: [-1.24 to 0.54]) using Cohen's d. The finding, although favouring intervention, was not statistically significant; a non-significant heterogeneity was also noted. Figure 5 illustrates the forest plot. In addition, a funnel plot did not reveal any publication bias, as shown in Figure 6.

The lack of a statistically positive effect for droperidol obviates further analysis of the need for rescue medication following its administration, patients' return to ED, and patient satisfaction.

IV. DISCUSSION

The benefits of butyrophenones as a treatment for patients presenting to ED with primary headaches appear significant. The changes in VAS scores, the total effect size of the reduction in VAS score by 25%, the reduced need for rescue medication, and the reduced incidence of patients returning to the ED, all hint at its effectiveness. Nonetheless, akathisia, agitation and anxiety were observed in one-third of the patients, and the effect on the QTc interval was difficult to ascertain. Taking a benefit/risk approach, haloperidol would continue to be a less desirable medication in this population.

From the perspective of patient satisfaction, such medication may be favoured as patients were less likely to return to ED and less likely to require rescue medication, indicating that their headache had improved. However, we believe that physicians who choose to use this class of drug should monitor patients for possible side effects, especially agitation and anxiety. Although we aimed in this analysis to examine haloperidol's effectiveness, other important drug safety should also be considered, including its use in those with severe cardiovascular disease, Myasthenia gravis, Parkinson and Thyroid dysfunction [29].

The effect of droperidol was analysed in two different groups by administering it IV/IM and measuring the VAS score. A comparison of the two groups demonstrated a negligible difference in VAS scores between those who received droperidol and those in the control group, which was not statistically significant.

Our results aligned with the findings of multiple systematic review studies that have been conducted on the effect of butyrophenones such as haloperidol and droperidol [30] [31] [32] [33].

Haloperidol's effect on the reduction of pain and the need for rescue medication was statistically significant and it was favoured by some patients, but the incidence of side effects was considerable. Reported side effects included akathisia, agitation, anxiety, and sedation. Thus, it is not recommended as a first-line treatment, but could be theorised. Based on the available evidence, we believe that haloperidol's negative effects should be taken into consideration before administering the medication. As for droperidol, most of the systematic reviews do not strongly recommend it [30] [31] [32] [33]; this medicine carries a considerable risk of side effects which is thought to exceed any potential advantage it might have in the short-term management of headaches.

V. LIMITATIONS

This analysis has an important limitation. We were unable to fully assess the risk of the studied medications on the QTc, as some of the included articles did not include an ECG in their methods and one article did not quantify the QTc in all of the patients.

VI. CONCLUSION

Haloperidol can induce a 25% reduction in VAS score for headache in the ED setting, as well as a 35% reduction in need for rescue medication, and improved patient satisfaction rate by 72%. The improvement was statistically significant; nonetheless, akathisia, agitation and anxiety were reported in 29.4% of patients who received haloperidol, while sedation was reported in 27.5%. Since the rate of return visits to the ED after receiving haloperidol could be as little as 6.42%, versus 11.5% in the control group, the benefit appears to outweigh the harm.

As for droperidol, the high risk of adverse reactions seems to outweigh any potential benefit it might offer for the short-term treatment of headaches.

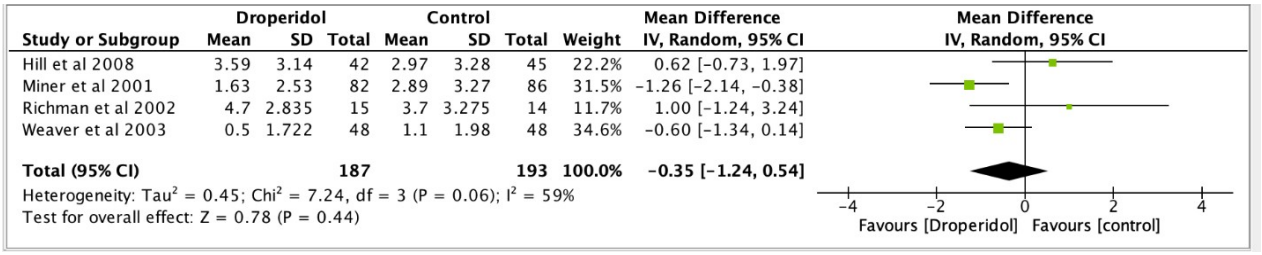

Figure 5. Forest plot of the effect of IM droperidol in patients with primary headache

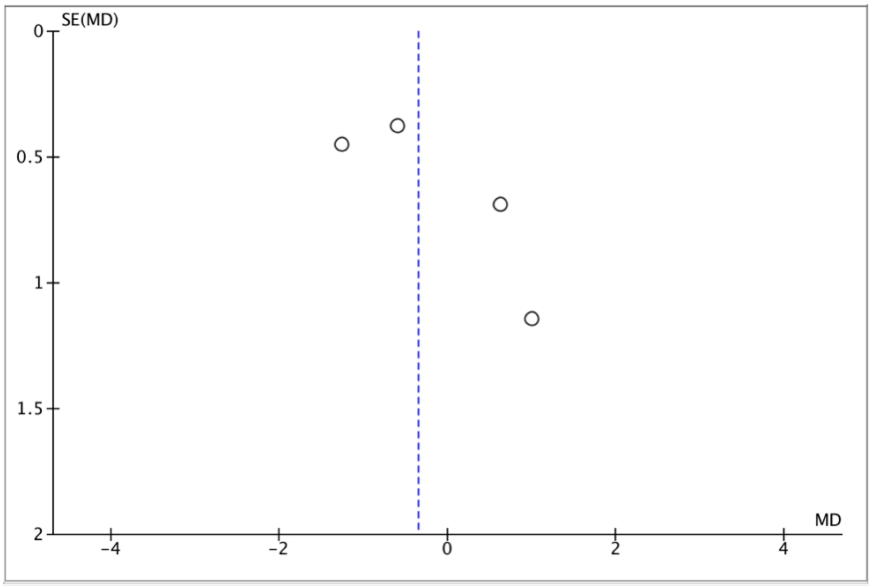

Figure 6. Funnel plot of included studies with a symmetrical distribution

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