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Robert M. Califf, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

We respectfully submit this Citizen Petition under 21 C.F.R. § 10.25(a), which allows individuals to ask the United States Food and Drug Administration (FDA) "[t]o issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."[1] Under administrative law, the FDA has adopted a flexible process of petitioning the FDA through a Citizen Petition as opposed to notice-and-comment rulemaking for labeling decisions on individual products. Under 21 U.S.C. § 352, the FDA has authority under the Food, Drug, and Cosmetic Act authority (FDCA) to regulate medication labels.[2] This request is accomplished through submitting a Citizen Petition for FDA consideration, under 21 C.F.R. § 10.30.[3] We are pharmacists in a health-system setting (Julie McCoy, Margaret McKenzie, Judith Kim, Minwoo Park, Zahra Abbasi, Tina Huynh-Pham, and Clarissa Munoz) supported by our Pharmacy and Therapeutics leaders, Dr. Alexander Kats and Dr. Harry Peled, to request an amendment to the droperidol boxed warning through this Citizen Petition.

A. Action Requested

This Citizen Petition requests that the FDA amend the droperidol boxed warning (also called black box warning, or BBW), to remove the following five sentences from the current boxed warning:

> "Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.
>
> Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is

[1] 21 C.F.R. § 10.25(a)
[2] 21 U.S.C. § 352
[3] 21 C.F.R. § 10.30

present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias."

Please see **Appendix A** for the entire text of the boxed warning, with proposed removal of sentences for this Citizen Petition amendment. The legal and factual grounds for this Citizen Petition are discussed below.

B. Statement of Grounds

Authority.

The FDA has the authority under the FDCA to regulate labels, as 21 U.S.C. Section 352 prohibits the misbranding of drugs, and labeling regulations are fundamental to the FDA.[2] Under the Citizen Petition process, the FDA carefully reviews proposed amendments and evidence to ensure the proper labeling of medications.

History of Droperidol Use.

Droperidol is a butyrophenone that was approved by the FDA in 1970, for clinical use as an antiemetic and as an adjuvant during general anesthesia.[4] It has existed for over 50 years, where it was the most commonly agent administered for nausea and vomiting for the last 30 years, with hundreds of millions of low doses given effectively and safely.[5,6]

Droperidol has the most post-marketing surveillance data among the currently approved antiemetic agents.[7] In 2001, the FDA required a boxed warning after evaluating 277 adverse events received from 1997 to 2002 that were reported as associated with droperidol. Reports to MedWatch claimed concerns for "reports of deaths associated with QT prolongation and torsades de pointes in patients treated with doses of Inapsine® (droperidol) above, within and even below the approved range." Of those cases, only two described adverse events were caused by droperidol dosages used in the United States.[8] The FDA drug advisory committee met in 2003 to provide clarity on droperidol's boxed warning label. It was concluded that there was insufficient data regarding the safety of lower doses than approved; therefore, the FDA requested Akorn Pharmaceuticals to undertake additional safety studies or extensive literature review.[9] The request was held off due to the pharmaceutical company's financial constraints. As a result, the FDA further stated that the boxed warning did not apply to doses of droperidol less than 2.5 mg because the use of droperidol at those doses were off label. The boxed warning was only for doses

[2] 21 U.S.C. § 352

[4] White PF et al. Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology*. 2005;102(6):1101-1105.

[5] Perkins J et al. American Academy of Emergency Medicine Position Statement: Safety of Droperidol Use in the Emergency Department. *J Emerg Med.* 2015;49(1):91-97.

[6] Gan TJ et al. FDA "black box" warning regarding use of droperidol for postoperative nausea and vomiting: is it justified?. *Anesthesiology*. 2002;97(1):287.

[7] Kramer KJ. The Surprising Re-emergence of Droperidol. *Anesth Prog*. 2020;67(3):125-126.

[8] Jackson CW et al. Evidence-based review of the black-box warning for droperidol. *Am J Health Syst Pharm*. 2007;64(11):1174-1186.

[9] Shale JH, Shale CM, Mastin WD. A review of the safety and efficacy of droperidol for the rapid sedation of severely agitated and violent patients. J Clin Psychiatry. 2003 May;64(5):500-5.

approved by the FDA because there was a lack of data submitted to the FDA to decide the safety and efficacy at doses less than 2.5 mg.

There has been a total of 708 studies published on PubMed about droperidol from year 2002 to 2021; of those studies, 153 are clinical trials, 21 are meta-analysis, and 147 are randomized controlled trials. Search terms in PubMed such as effective, efficacy, safety, safe, and low dose droperidol showed 542, 129, 116, 48, and 49 studies that resulted respectively. Position statements by the American College of Emergency Physicians, the American Academy of Emergency Medicine[10], and the Anesthesia Patient Safety Foundation has also been published addressing droperidol. Within this Citizen Petition, we ask the FDA to review the newest data regarding the safety and efficacy of droperidol, including at low doses, and to revise the boxed warning placed in 2001.

Sources Used to provide evidence that Droperidol is safe and efficacious

A literature search was conducted from 1999 to 2020 with key words of droperidol/Inapsine®. All the literature identified during our review is available in **Appendix B**; Randomized controlled trials (RCTs), observational retrospective or prospective trials and literature reviews, along with information stating the droperidol is a safe and effective medication were used to support our petition. The level of evidence was assigned a grade using the definitions noted in Table 1 and were based by the Cochrane systematic reviews and the American Academy Emergency Medicine Position Statement by Perkins et al.[5, 11] The risk of bias was assessed by, but not limited to, allocation concealment, blinding, and free of selective reporting. If an article had high risk of bias, the grade was decreased despite the definition of the grade.

Table 1. Definition of the Grades of Evidence of the Articles[5]

Grade	Definition
A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue
B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
B-U	Prospective, controlled, nonrandomized, retrospective, cohort, or case-control studies
U	Case series or case reports, unreferenced opinion in literature, or common practice

Of note, some of the articles or sources used did not apply to the comparator's table but provided evidence used within this petition to further support our action requested (Table 2).

[10] Use of Droperidol in the Emergency Department. American College of Emergency Physicians. Published March 2021. Accessed December 19, 2021.

5 Perkins J et al. American Academy of Emergency Medicine Position Statement: Safety of Droperidol Use in the Emergency Department. J Emerg Med. 2015;49(1):91-97.

[11] GRADE approach. Accessed March 31, 2022. https://training.cochrane.org/grade-approach

Table 2. Factors that may decrease the quality level of a body of evidence.[11]

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide confidence intervals).
5. High probability of publication bias.

Labeling of boxed warning should be less than 20 lines.

Labeling of Prescription Drugs is outlined in 21 C.F.R. § 201, and boxed warnings shall contain format and labeling as described in 21 C.F.R. § 201.57.[12]

> "(4) *Boxed warning.* A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."[11]

The current droperidol boxed warning on the American Reagent package insert includes 24 lines of text, exceeding the recommended length of 20 lines. The current language includes the heading, "WARNING", but does not contain the verbatim statement after the heading of the boxed warning stating "See full prescribing information for complete boxed warning."

The current boxed warning includes two sentences that are very similar in stating the risk that droperidol has been shown to cause QT prolongation and/or torsade de pointes. The first sentence states, "[c]ases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses." The redundant sentence that is recommended for removal is "Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol." This repetitive statement should be removed to enhance the brevity of the boxed warning language, as outlined in 21 C.F.R. § 201.57(c)(1). See Boxed Warning in Appendix A. This sentence is redundant and should be removed, as the very first sentence of the boxed warning delivers the same message by stating, "[c]ases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses."

Removing redundant language and language that does not meet the intent of boxed warnings will bring the boxed warning into compliance with 21 C.F.R. § 201.57(4).

The additional four sentences requested to be removed by this Citizen Petition amendment do not meet the intent of a boxed warning and will be discussed under the next sections.

[12] 21 C.F.R. § 201.57(a)(4)

Risk should be briefly outlined in the boxed warning.
The boxed warning "must briefly explain the risk," as outlined in 21 C.F.R. § 201.57(c)(1).

> *(1) Boxed warning.* Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.[13]

The current boxed warning is compliant in stating that droperidol poses a risk of QT prolongation and/or torsade de pointes. However, the boxed warning overstates the risk with prescriptive monitoring requirements and fails to convey a general focus with a reference to the other sections of the package insert with more detailed information. Please see **Appendix A** for the entire text of the boxed warning, with proposed removal of sentences for Citizen Petition amendment.

The labeling requirements under 21 C.F.R. § 201.57(c)(1) should briefly outline the general focus of the risk. The third sentence of the boxed warning goes beyond the general focus of the risk and advises prescribers of when to use droperidol, which is outside the scope of an evidence-based factual boxed warning.

The third sentence of the boxed warning is over-prescriptive toward providers who determine droperidol to be a clinically relevant agent, "Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs." This sentence is over-prescriptive in that it does not differentiate that droperidol should be reserved in a specific high-risk patient population, with language that recommends prescribing restrictions in all patients.

Boxed warnings should not be prescriptive, as the labeling requirements under 21 C.F.R. § 201.57(c)(1) are to convey the general focus of risk information and refer to the "Contraindications" or "Warnings and Precautions" sections.

The Warnings section of the droperidol package insert (American Reagent example; **Appendix A**) advises on the recommendation for ECG monitoring, based on the potential for droperidol to impact cardiac conduction. The language recommended to be removed through this Citizen Petition is exactly the same as the elaborate text stated in the Warnings section of the package insert.

The intent of the boxed warning is to briefly outline the risk and refer to more detailed information in the other sections. Here, the following sentences are overly prescriptive and redundant for the boxed warning, which should convey the general focus and refer to the prescriptive language that is already stated in the "Warnings" section,

[13] 21 C.F.R. § 201.57(c)(1)

> "[b]ased on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias."

Removal of this prescriptive and redundant statement from the boxed warning, with referral to the "Warnings" section more closely aligns with 21 C.F.R. § 201.57, briefly outlining the risk of droperidol. Therefore, this Citizen Petition requests the removal of these sentences from the boxed warning. See Boxed Warning in Appendix A.

Efficacy of Droperidol is demonstrated.

Droperidol works in the chemoreceptor trigger zone, achieving most of its anti-emetic effects through potent dopamine D_2 receptor inhibition.[5] Other effects of droperidol are produced through mild alpha-adrenergic inhibition that causes peripheral vascular dilatation and reduces the effects of epinephrine. Until the emergence of 5-HT_3 antagonists (e.g., ondansetron, granisetron, dolasetron, and palonosetron) droperidol was the first-line antiemetic for the treatment and prevention of post-operative nausea and vomiting (PONV). Since then, studies have shown droperidol in combination with ondansetron has repeatedly outperformed either agent alone for PONV prevention, without significant side effects.[14] The efficacy of droperidol has continued to be demonstrated in PONV or as an add-on adjunctive therapy with an opioid analgesic to aid in tranquilization.[15]

Droperidol is effective in emergent settings, as it has a rapid onset of action.[16] It is available to be given intramuscularly or intravenously and readily crosses the blood-brain barrier. The onset of action of single intramuscular (IM) and intravenous (IV) doses is from three to ten minutes following administration, although the peak effect may not be apparent for up to thirty minutes. The duration of the tranquilizing and sedative effects generally is two to four hours.

The known adverse effects are sedation, extrapyramidal symptoms (dystonia, akathisia, oculogyric crisis), hypotension, tachycardia, dysphonia.[5] Unfortunately, the driver of the box warning was due to droperidol's ability to cause QT prolongation by blocking the potassium efflux from myocardial cells which disrupts membrane repolarization thus increasing cardiac complications.[17]

Several studies compare droperidol to other agents as an effective antiemetic, chemical restraint, and agent for treatment of acute headache. Studies have also analyzed the effectiveness of droperidol in different clinical settings (i.e., emergency department or post-anesthesia care units). Moreover, studies demonstrate whether low dose droperidol is an efficacious option to reduce the adverse effects stated

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[5] Perkins J et al. American Academy of Emergency Medicine Position Statement: Safety of Droperidol Use in the Emergency Department. *J Emerg Med.* 2015;49(1):91-97.

[14] Matsota P et al. Ondansetron-droperidol combination vs. ondansetron or droperidol monotherapy in the prevention of postoperative nausea and vomiting. *Arch Med Sci*. 2015;11(2):362-370.

[15] Ludwin DB et al. Con: The black box warning on droperidol should not be removed (but should be clarified!). *Anesth Analg*. 2008;106(5):1418-1420.

[16] Droperidol Use in the Emergency Department – What's Old is New Again. emDOCs.net - Emergency Medicine Education. Published August 1, 2019. Accessed January 18, 2022.

[17] Kao LW et al. Droperidol, QT prolongation, and sudden death: what is the evidence?. *Ann Emerg Med*. 2003;41(4):546-558.

in the box warning. Here we discuss the evidence supporting droperidol's efficacy in these indications, clinical settings, and in low doses.

Efficacy: Droperidol for Nausea and Vomiting

The FDA-approved indication for droperidol is PONV, which evidence is demonstrated that it is an effective antiemetic.[18,19] When droperidol was used in a factorial trial for the prevention of PONV, it reduced symptoms by 26%, non-inferior to its comparators; ondansetron and dexamethasone.[20] In comparison to metoclopramide, prochlorperazine and saline placebo, droperidol significantly reduced nausea at 30 min compared to metoclopramide and prochlorperazine ($P = 0.04$) showing that it was significantly better at controlling moderate-to-severe nausea in ED patients.[21] Another study comparing ondansetron 4 mg IV, droperidol 0.625 mg IV, droperidol 1.25 mg IV, and placebo injection found droperidol at 1.25 mg required the least amount of rescue antiemetic or emesis ($P < 0.05$).[19] Lastly, when droperidol was combined with ondansetron, it had higher efficacy vs droperidol and ondansetron monotherapy.[14]

Furthermore, the American College of Emergency Physicians policy statement stated that a study by Meek et al has shown the potential superiority of droperidol for treating nausea and vomiting in the ED setting. In this study, droperidol achieved the desired treatment effect 77% vs. 59% (ARR = 18%; 95% CI 3 to 13%; NNT=5).[22]

It is confirmed that droperidol relieves nausea and vomiting symptoms either faster or equivalent to placebo or comparator agents. Some of these studies have used droperidol at lower than recommended doses where it is apparent that droperidol can be potentially used in lower doses. Additional evidence demonstrating efficacy of low-dose droperidol will be discussed below.

Efficacy: Droperidol Use in the Treatment of Agitation/Sedation

There are several studies comparing droperidol to other classes of sedating medications or placebo to determine efficacy of use in agitated patients. The DORM study looked at droperidol vs midazolam for sedation of 91 emergency department patients with violent and acute behavioral disturbances.[23] They randomized patients to droperidol, midazolam, or a combination of the two medications (33 received droperidol, 29 received midazolam, and 29 received combination) and found that there was no difference in the median duration (20 minutes for droperidol, 24 minutes for midazolam, and 25 minutes for the combination).

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[18] Kreisler NS et al. Small-dose droperidol effectively reduces nausea in a general surgical adult patient population. *Anesth Analg.* 2000;91(5):1256-1261.

[19] Fortney JT et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. *Anesth Analg*. 1998;86(4):731-738.

[20] Apfel CC et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*. 2004;350(24):2441-2451.

[21] Braude D et al. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. Am J Emerg Med. 2006;24(2):177-182.

[14] Matsota P et al. Ondansetron-droperidol combination vs. ondansetron or droperidol monotherapy in the prevention of postoperative nausea and vomiting. *Arch Med Sci*. 2015;11(2):362-370.

[22] Meek R et al. Randomized Placebo-controlled Trial of Droperidol and Ondansetron for Adult Emergency Department Patients With Nausea. *Acad Emerg Med*. 2019;26(8):867-877.

[23] Isbister GK et al. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med*. 2010;56(4):392-401.e1.

Furthermore, additional sedation was required in the midazolam group; 11 (33%; 95% confidence interval [CI] 19% to 52%) droperidol patients, 18 (62%; 95% CI 42% to 79%) midazolam patients, and 12 (41%; 95% CI 24% to 61%) in the combination group. Overall, droperidol was non-inferior to midazolam for the duration of violent and acute behavioral disturbances and required less additional administrated doses for optimal sedation in agitated patients.

Similarly, Chan and colleagues performed a clinical trial of 336 patients who were randomized to receive either a saline solution (control), droperidol (5 mg), or olanzapine (5 mg) bolus to midazolam for acute agitation in emergency department.[24] In this study, they have found that droperidol and olanzapine sedation rates were significantly shorter than the placebo group. Chan and colleagues have also demonstrated that droperidol (12.5%) required less need for additional parenteral sedating drugs to reach initial adequate sedation vs olanzapine (16.5%) need for concurrent midazolam in the acutely agitated.

In addition, Page and colleagues performed a prospective before and after study comparing droperidol to midazolam for pre-hospital acute behavioral disturbance. They found that droperidol had a shorter median time to sedation of 22 minutes than midazolam at 30 minutes.[25] Therefore, the evidence of droperidol's effectiveness in sedation is comparable to other agents.

Additionally, a systematic review performed by Gottlieb and colleagues found six clinical trials that compared placebo, haloperidol, olanzapine, midazolam, and droperidol to patients with agitation.[26] In this review, two randomized controlled trials comparing droperidol and haloperidol found that droperidol was associated with a decreased need for additional medication for sedation after 60 minutes (risk ratio=0.37; 95% CI 0.16-0.90). Moreover, midazolam and olanzapine were no different from droperidol in requiring supplemental medication at 60 minutes. Overall, this review demonstrated that droperidol is a rapid and effective agent for the treatment of agitation in the ED setting.

In conclusion, these studies have demonstrated that droperidol is an effective agent for sedation and agitation.

Efficacy: Droperidol Used in the Treatment of Headache

Droperidol has been evaluated in the management of both migraines and tension-type headaches.[27] Seventy-three cases were reviewed in the ED setting where they received droperidol at doses less than 2 mg and found that 73% had complete resolution or significant improvement of headache symptoms as subjectively or objectively.[27] When droperidol was compared to prochlorperazine for benign headaches in the ED, droperidol reduced symptoms of

[24] Chan EW, et al. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med*. 2013;61(1):72-81.

[25] Page CB, et al. A Prospective Before and After Study of Droperidol for Prehospital Acute Behavioral Disturbance. *Prehosp Emerg Care*. 2018;22(6):713-721.

[26] Gottlieb M, et al. What Is the Efficacy of Droperidol for the Management of Acute Psychosis-Induced Agitation?. *Ann Emerg Med*. 2018;71(1):141-143.

[27] Faine B, et al. Treating primary headaches in the ED: can droperidol regain its role?.*Am J Emerg Med*. 2012;30(7):1255-1262.

headaches within 60 minutes (p=0.001).[28] Similarly, another study also compared droperidol and prochlorperazine and found that at 60 minutes pain reduction in the droperidol group was significantly more reduced than the prochlorperazine group (83.3% vs 72.3%; P < 0.01).[29] These results have found that droperidol patients received more relief for their headaches and did not suffer any significant side effects versus their comparators.

Additionally, a pilot study in 1999 conducted a retrospective case series of ED patients with acute migraine who received IM droperidol and found 81% of the patients found relief.[30] Overall, droperidol given IM may be a safe and effective therapy for the ED to manage acute migraine headache.

It is evident that droperidol has multipurpose indications that are comparable to other agents for several indications like headache and migraines.

Efficacy: Droperidol Used in low doses (less than 2.5 mg)

As discussed above, droperidol has been used for many indications off-label with lower dosages than FDA approved.[31] Droperidol is FDA approved at 2.5 mg, 5 mg, and 10 mg. Doses under 2.5 mg, such as 0.625 mg or 1.25 mg, are considered off-label.[32] However, the first sentence by the FDA warning indicates that there are significant risk with droperidol, even at low doses, stating, "[c]ases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses." Therefore, there is confusion on whether lower doses require monitoring, and recommendations in this Citizen Petition align with evidence to support the safe use of efficacious lower droperidol doses.

Of note, there has been clarification of the box warning in 2003, where the FDA announced that the boxed warning did not apply for doses of droperidol less than 2.5 mg. However, the FDA had no comment on the safety and efficacy of the low doses of droperidol due to the lack of data submitted to the FDA.[31,33] This statement was again reiterated in 2008.

Since that time, there have been data supporting the efficacy of doses of 0.625 mg and 1.25 mg of droperidol. In this section we will be discussing the trials that have been published determining that low dose droperidol is efficacious.

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[28] Miner JR, et al. Droperidol vs. prochlorperazine for benign headaches in the emergency department. *Acad Emerg Med*. 2001;8(9):873-879.

[29] Weaver CS, et al. Droperidol vs prochlorperazine for the treatment of acute headache. *J Emerg Med*. 2004;26(2):145-150.

[30] Richman PB, et al. Droperidol for acute migraine headache. *Am J Emerg Med*. 1999;17(4):398-400.

[14] Matsota P et al. Ondansetron-droperidol combination vs. ondansetron or droperidol monotherapy in the prevention of postoperative nausea and vomiting. Arch Med Sci. 2015;11(2):362-370.

[19] Fortney JT et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesth Analg. 1998;86(4):731-738.

[21] Braude D et al. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. Am J Emerg Med. 2006;24(2):177-182.

[31] Cure S, et al. Droperidol for acute psychosis. *Cochrane Database Syst Rev*. 2004;(4):CD002830. Published 2004 Oct 18.

[32] Rappaport BA. FDA response to droperidol black box warning editorials. *Anesth Analg*. 2008;106(5):1585.

[18] Kreisler NS et al. Small-dose droperidol effectively reduces nausea in a general surgical adult patient population. Anesth Analg. 2000;91(5):1256-1261.

In a prospective, randomized, placebo-controlled study, determined whether low doses of IV droperidol at 0.625 mg given 30 min before general anesthesia reduces the incidence of immediate and delayed PONV in a general surgical adult patient population.[18] They compared the efficacy of droperidol, ondansetron, and promethazine for the rescue treatment of PONV. Compared to placebo, droperidol was superior in the incidence of PONV vs placebo (P<0.001).[18] Those who received rescue treatment of PONV, droperidol was associated with fewer requests for a second antiemetic, but statistical power was insufficient to reach significance (P = 0.613).[18]

Several other studies that used droperidol in low doses for PONV and compared it against ondansetron, metoclopramide, and prochlorperazine.[14, 19, 21] These studies have found that droperidol monotherapy or combination therapy with ondansetron significantly decreased symptoms of PONV.

Another randomized double-blinded study has found that droperidol at low doses has opioid-sparing effects.[34] In this study, morphine was used significantly less in the droperidol group vs the control group and additionally, the droperidol group had less PONV. The doses they used in this study was 50 mcg.

To conclude, droperidol in low doses is just as effective and efficacious when compared to other agents utilized for nausea and vomiting. The above literature does not demonstrate evidence mandating an ECG or telemetry monitoring for doses less than 2.5 mg. Thus, the recommended removal of five sentences from the boxed warning in this Citizen Petition provides clarity for Providers who utilize evidence-based low-dose droperidol, because the revised boxed warning would be less prescriptive, relevant, and apply to all doses of droperidol.

Safety of Droperidol is demonstrated (current boxed warning includes safety warning).

Safety of droperidol was questioned when the FDA issued a boxed warning for droperidol due to 277 MedWatch case reports. Jackson et al published a review of the case reports based on information they received from FDA. [8] Of the 277 case reports, many of them were either repeat reports or reports outside of the US with supratherapeutic doses of droperidol leading to death. Nevertheless, there were 11 cases of torsades de pointes. Of the five patients, 4 of the 5 deaths were reports outside of the US and the one death in the US was a patient who received droperidol 3.75 mg IV and concomitant vasopressin and nitroglycerin.[35]

Of the 6 reports who survived from torsades de pointe, 3 were hospitalized, and 3 suffered life-threatening adverse effects. One of the cases that received low dose droperidol at 0.625 mg was hospitalized but had cardiovascular complications and had history of taking medications that may prolong QT like fluoxetine and metoclopramide.[8]

[34] Lo Y, et al. Morphine sparing with droperidol in patient-controlled analgesia. *J Clin Anesth*. 2005;17(4):271-275.
[8] Jackson CW et al. Evidence-based review of the black-box warning for droperidol. Am J Health Syst Pharm. 2007;64(11):1174-1186.
[35] Mattson A, Friend K, Brown CS, Cabrera D. Reintegrating droperidol into emergency medicine practice. Am J Health Syst Pharm. 2020;77(22):1838-1845.

Since the relabeling of the boxed warning, several safety studies have been published that warrant an amendment to the boxed warning. These studies also demonstrate that the boxed warning is overstated for the risks posed at the doses used.

Safety: QT Interval Prolongation Risk with Droperidol

QT interval prolongation is commonly used as a surrogate marker for the risk of torsade de pointes. Several studies have found that the incidence of droperidol-induced QT prolongation is similar to comparators, such as haloperidol and ondansetron. This was described in a randomized, double-blinded controlled study conducted by Tracz et al. assessing the effects of droperidol on the parameters of cardiac repolarization.[36] This study found that doses of droperidol 1.25 mg caused slight but transient QT prolongation, which ultimately did not affect cardiac repolarization. The study also compared droperidol doses of 0.625 mg vs ondansetron 8 mg, where they observed there were no differences between droperidol and ondansetron in QT prolongation.

Other studies have also shown similar QT prolongation rates, for example, Macht et al. assessed QT interval changes after droperidol administration which found similar rates between droperidol and haloperidol, 453 ms (range 398-542) versus 448 ms (range 386-542), respectively.[37] These studies support the statement that droperidol does not produce more QT prolongation than other medications.

In a randomized, double blinded, placebo-controlled study, White et al. compared the safety of droperidol 0.625 mg, droperidol 1.25 mg, and saline, and found that neither of the droperidol treatment groups significantly prolonged the QT interval in comparison to saline, 15±40 ms, 22±41 ms, and 12±35 ms, respectively.[4] The study did find that these small doses of droperidol produced greater than 10% QT prolongation in 10-15% of the patients; however, the effect was transient, not statistically significant, and did not lead to cardiac arrhythmia.

Chan et al undertook a randomized, double-blind, placebo-controlled clinical trial with 336 patients requiring intravenous drug sedation for acute agitation who were randomized to receive a saline solution, droperidol 5 mg, or olanzapine 5 mg bolus.[24] This was immediately followed by incremental intravenous midazolam boluses (2.5 to 5 mg) until sedation was achieved. The primary outcome was time to sedation, and secondary outcomes were need for "rescue" drugs and adverse events. An ECG was obtained within 60 minutes of initial adequate sedation for 211 (62.8%) patients: 62 (53.9%), 77 (68.8%), and 72 (66.1%) in the control, droperidol, and olanzapine groups, respectively. The median QTc intervals did not differ between groups: control 444 msec (interquartile range [IQR] 425 to 461 msec), droperidol 441 msec (IQR 421 to 460 msec), and olanzapine 448 msec (IQR 426 to 462 msec). Two patients had a QTc interval greater than or equal to 500 msec, 1 in the control group (500 msec) and 1 in the

[36] Tracz K, et al. Small doses of droperidol do not present relevant torsadogenic actions: a double-blind, ondansetron-controlled study. *Br J Clin Pharmacol*. 2015;79(4):669-676.
[37] Macht M, et al. Comparison of droperidol and haloperidol for use by paramedics: assessment of safety and effectiveness. *Prehosp Emerg Care*. 2014;18(3):375-380.
[4] White PF et al. Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology*. 2005;102(6):1101-1105.
[24] Chan EW, et al. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med*. 2013;61(1):72-81.

olanzapine group (512 msec). Neither patient experienced an adverse event related to the prolonged QTc.

Safety: QT Interval Prolongation Risk with Low-Dose Droperidol

The most recent cohort study assesses the QTc interval variation after low-dose (≤ 2.5 mg) droperidol in undifferentiated, stable, and non-agitated patients.[38] They found that the mean maximum delta of QTc interval after droperidol across all 68 patients was +29.9 ms (SD 15). A total of 12 patients (17.6%) experienced a QTc interval ≥ 500 ms during the observation period after droperidol, and 3 patients (4.4%) had a delta QTc ≥ +60 ms. Overall, no serious arrhythmias or deaths among the 68 participants in this study. There was only non-serious adverse events (13.2%) had at least one non-serious adverse event that includes restlessness and/or anxiety.[38]

Safety: Torsade de Pointes and Arrhythmia Risk with Droperidol

Several studies demonstrated that the administration of droperidol did not significantly increase the risk of torsade de pointes. For instance, Cole et al. determined that in both noncritical and critically ill patients the torsade de pointes rates were low and had most likely been caused by other risk factors.[39] In this study, 15,374 noncritical patients received 18,020 doses of droperidol, and of the 11,583 critically ill patients 1,172 patients received droperidol. Among the patients who received droperidol, there was only a single case of torsade de pointes, which occurred in a patient with risk factors such as alcohol use disorder and hypomagnesemia. Therefore, the incidence of torsade de pointes was 1/16,546 (0.006%; 95% CI, 0.00015 - 0.03367%). These studies support the statement that droperidol does not produce more QT prolongation than other medications nor did droperidol cause fatal arrhythmias. This evidence supports the Citizen Petition recommendation to amend the boxed warning, since the incidence of torsade de pointes was minimal and not caused by droperidol.

Other studies have produced similar data, describing the low frequency of torsade de pointes or fatal arrhythmias. For example, Calver et al. conducted a prospective observational study in six EDs where patients received droperidol with median total.[40] It is important to note that seven of the 13 patients had additional QT-prolonging confounders (methadone, escitalopram, amiodarone, or preexisting prolonged QTc interval). There were 71 adverse events in 70 patients (70/1,403 [5.0%]; 95% CI 3.9% to 6.3%), with one patient having two adverse events. The more common adverse events were hypotension (28 patients) and desaturation (22 patients). There is no evidence of increased risk for QT prolongation with the doses used in this study. In addition, there were no cases of torsades de pointes in the larger cohort of 1,403 patients, suggesting that the risk of torsades de pointes is less than 0.3% according to the size of the cohort. This study suggests that droperidol in doses of 10 to 20 mg is highly unlikely to cause QT prolongation, further supporting the statement that the boxed warning overestimates the risk of droperidol, and patients do not need routine ECGs after receiving droperidol.

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[38] Hernández-Rodríguez L, Bellolio F, Cabrera D, et al. Prospective real-time evaluation of the QTc interval variation after low-dose droperidol among emergency department patients. Am J Emerg Med. 2022;52:212-219. doi:10.1016/j.ajem.2021.12.039

[39] Cole JB, et al. The Incidence of QT Prolongation and Torsades des Pointes in Patients Receiving Droperidol in an Urban Emergency Department. *West J Emerg Med*. 2020;21(4):728-736.

[40] Calver L, et al. The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department. *Ann Emerg Med*. 2015;66(3):230-238.e1.

Safety: Torsade de Pointes and Arrhythmia Risk with Low-Dose Droperidol

Nuttall et al. conducted a retrospective study to determine if low-dose (0.625 mg) droperidol administration was associated with episodes of torsade de pointes in the general surgical population.[41] The authors identified 20,000 patients who received over 35,000 doses of droperidol (0.625 mg). The patients were cross-matched with an electrocardiogram database and an adverse outcome database. The charts of 858 patients were reviewed, including patients with documentation of prolonged QTc (>440 ms), polymorphic ventricular tachycardia (VT) within 48 hours of receiving droperidol, or death within seven days of receiving droperidol. Twelve out of 20,122 surgical patients had VT (n=4; event rate = 2.0 per 10,000, 95% CI 0.5 to 5.1 per 10,000) or died (n = 8; event rate = 4.0 per 10,000, 95% CI 1.7 to 7.8 per 10,000) within 48 hours of droperidol administration. There were no patients who clearly developed polymorphic VT or died due to droperidol administration (n = 0; event rate = 0.0 per 10,000, 95% CI 0.0 to 1.8 per 10,000). All of the eight patients who died were on palliative care and died of their disease. The four patients with documented VT had previous cardiac conditions. The data suggested that low-dose droperidol does not increase the incidence of polymorphic VT or death when used to treat PONV in the surgical population. Also, data suggest that ventricular tachycardia induced by droperidol, if it exists, to be rare.

Systemic Review of Overall Safety and Efficacy of Droperidol

Gottlieb et al. undertook a systematic review of 14 studies, of which six (n=733 total patients) met the inclusion criteria comparing droperidol with haloperidol, olanzapine, midazolam, and placebo for acute psychosis-induced agitation in emergency, inpatient psychiatric or other medical settings showed more patients with droperidol were sedated within 30 minutes.[25] There was no difference in time to sedation in all agents. Droperidol was associated with a decreased risk of needing additional medication after 60 minutes in comparison to haloperidol. Droperidol is effective for the treatment of acute psychosis-induced aggression or agitation, with a low risk of adverse events compared with placebo, olanzapine, haloperidol, and midazolam. Overall, this review suggests that droperidol is safe and effective for the treatment of acute agitation in the ED setting, with low rates of QT prolongation and no cases of torsades de pointes.

In summary, the clinical trials have proven that droperidol is as safe as other QT prolonging medications stated above and droperidol does not cause fatal arrhythmias. Safety data spans FDA approved doses and lower doses as well. Therefore, the studies above support the claim that the boxed warning is overstated, and an amendment is necessary.

C. Environmental Impact

a. Under 21 C.F.R. § 25.31, this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact

a. According to 21 C.F.R. § 10.30, economic impact information will be provided if requested by the Commissioner following review of this petition.

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[41] Nuttall GA, et al. Does low-dose droperidol increase the risk of polymorphic ventricular tachycardia or death in the surgical patient?. *Anesthesiology*. 2013;118(2):382-386.

[25] Gottlieb M, Schiebout J. What Is the Efficacy of Droperidol for the Management of Acute Psychosis-Induced Agitation?. Ann Emerg Med. 2018;71(1):141-143.

E. Conclusion

Under 21 U.S.C. § 352, the FDA has authority under the Food, Drug, and Cosmetic Act (FDCA) to regulate medication labels, including boxed warnings[2]. Under the Citizen Petition process, the FDA carefully reviews proposed amendments and evidence to ensure the proper labeling of medications. Labeling of Prescription Drugs is outlined in 21 C.F.R. § 201, and boxed warnings shall contain format and labeling as described in 21 C.F.R. § 201.57.[11] The boxed warning "must briefly explain the risk," as delineated in 21 C.F.R. § 201.57(c)(1).

The current boxed warning is shown in Appendix A. The boxed warning exceeds the recommended length of 20 lines, as defined in 21 C.F.R. § 201.57.[11]

The current language in the boxed warning is redundant and over prescriptive, where the boxed warning "must briefly explain the risk," as summarized in 21 C.F.R. § 201.57(c)(1).

There is evidence from randomized, controlled trials, observational studies, and meta-analyses demonstrating that droperidol is a safe and effective drug that does not require a prescriptive boxed warning for FDA approved doses and lower doses. Here, we are proposing removal of five sentences from the current droperidol boxed warning, to explain potential risks with brevity, reduce redundancies, apply evidence demonstrating that droperidol is effective, and apply evidence that droperidol is safe at both FDA approved doses and at lower doses.

This Citizen Petition requests that the FDA amend the droperidol boxed warning, to remove the following five sentences from the current boxed warning:

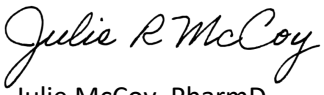
> "Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.
>
> Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias."

[2] 21 U.S.C. § 352
[11] 21 C.F.R. § 201.57(a)(4)

F. Certification

We certify that, to our best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) We have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to us.

Sincerely,



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Appendix A

WARNING[42]

Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

~~**Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.**~~

~~**Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias.**~~

Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. Droperidol should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and IV opiates.

Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect

[42] American Reagent's Package Insert

Appendix B

Comparative Evidence Tables

Bias Assessment:	**Study Grades:**	**Abbreviations:**	
Low risk: Plausible bias unlikely to seriously alter the results. **Uncertain risk:** Plausible bias that raises some doubt about the results. **High risk:** Plausible bias that seriously weakens confidence in the results.	**Grade A:** Useful **Grade B:** Possibly Useful **Grade B-U:** Possible to Uncertain Usefulness **Grade U:** Uncertain Validity and/or Usefulness	**ASA** = American Society of Anesthesiologist **AMSS** = Altered Mental Status Scale **BBW** = black box warning **BVM** = bag–valve–mask **CI** = confidence interval **ECG/EKG** = electrocardiogram **ED/ER** = Emergency department/room **ms** = miliseconds **mg** = milligrams **mcg** = micrograms **OR =** odds ratio **RCT =** randomized controlled trial **NNT** = number needed to treat	**NS =** normal saline **N/V** = nausea and vomiting **RR =** risk reduction; relative risk **ITT =** intention to treat **IQR** = Interquartile range **PACU** = postanesthesia care unit **PCA** = patient-controlled analgesia **PONV** = post-operative nausea and vomiting **VAS** = visual analog scale **TdP** = Torsades de Pointe **ECG** = Electrocardiogram **VRSC** = verbal rating score during cough or movement **VRSR** = verbal rating score at rest

Direct Comparative Evidence Table

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or Very Low** ⊕□□□
Author: Matsota et al., 2015 Title: Ondansetron-droperidol combination vs. ondansetron or droperidol monotherapy in the prevention of postoperative nausea and vomiting Comparator: Group Droperidol	Prospective, randomized, double blinded study was approved by the Medical Ethics Committee of the "Attikon" University Hospital, Athens, Greece (n=127)	Inclusion: All participants undergoing elective laparoscopic cholecystectomy between August 2007 and August 2010 Exclusion: Obesity class III (body mass index ≥ 40 kg/m2), past medical history of motion sickness, diabetes mellitus, intake of opioids and antiemetics during the previous month, and episodes of emesis 24h preoperatively	Primary Endpoint: • Number of patients experiencing PONV • Percentage of patients with a complete response (no N/V) during the 24h postop period • Number of patients who required rescue antiemetic medication Secondary Endpoint: • Cost analysis of the antiemetic management • Safety profile of the administered prophylactic antiemetic drugs • Patient's overall satisfaction regarding PONV pretreatment Results: • Total of 127 patients: 40 in group D, 40 in group O and 47 in group D + O.	**GRADE:** A **QUALITY OF EVIDENCE (GRADE):** High ⊕⊕⊕⊕ **ASSESSMENT:** Low risk **STRENGTHS:** Combination therapy with droperidol and ondansetron is more effective in the prevention of PONV than monotherapy. There are no differences in the distribution amount groups regarding gender and smoking status. Anesthetic and surgical factors associated with PONV were balanced among groups. All patients underwent laparoscopic cholecystectomy was by the same team of anesthetists and surgeons. Duration of

(D): 1.25 mg of droperidol (IV) at the end of the surgery
Group Ondansetron (O): 4 mg of ondansetron (IV) at the end of the surgery
Group D + O: combination of droperidol and ondansetron given iv

Primary Outcomes:

- 35 patients experienced vomiting in group D and 30 patients experienced vomiting in group O
- 11 patients experienced vomiting in group D + O ((D + O vs. D, $p < 0.05$), (D + O vs. O, $p < 0.05$))
- Combination therapy was significantly more effective than monotherapy with both agents in preventing PONV at 30 min, 3 h and 6 h postoperatively (Table 1)
- Ondansetron was more effective in preventing PONV at 30 min, 3 h, 6 h postoperatively (Table 1)
- Percentage of patients with a complete response (no nausea and no vomiting) during the 24-hour postoperative period was significantly greater in group D + O (38%) than in groups D (3%, $p < 0.01$) and O (5%, $p < 0.01$)

Table 1: Number of patients (%) with nausea or vomiting and nausea scores after laparoscopic cholecystectomy.

Time after surgery	Group D (*n* = 40)	Group O (*n* = 40)	Group D + O (*n* = 47)
0–30 min:			
Nausea (%)	19 (47.5)	10 (25)	8 (17)
Vomiting (%)	11 (27.5)	8 (20)	0 (0)
Total PONV	30 (75)	18 (45)	8 (17)[*†]
Nausea score	0.85 ±0.718	0.72 ±1.170	0.38 ±0.898
30–60 min:			
Nausea (%)	5 (12.5)	7 (17.5)	16 (34.0)
Vomiting (%)	1 (2.5)	2 (5)	1 (2.13)
Total PONV	6 (15)	9 (22.5)	17 (36.2)
Nausea score	0.54 ±0.844	1.03 ±1.44	0.58 ±0.794
1–3 h:			
Nausea (%)	18 (45)	18 (45)	20 (42.5)
Vomiting (%)	21 (52.5)	18 (45)	10 (21.3)
Total PONV	39 (97.5)	36 (90)	30 (63.8)[*§]
Nausea score	1.37 ±0.761	1.55 ±1.143	0.780 ±0.917[≠]
3–6 h:			
Nausea (%)	17 (42.5)	6 (15)	3 (6.4)
Vomiting (%)	2 (5)	2 (5)	0 (0)
Total PONV	19 (47.5)	8 (20)[‡]	3 (6.4)[*]
Nausea score	0.45 ±0.504	0.53 ±1.246	0.170 ±0.670
6–12 h:			
Nausea (%)	4 (10)	0 (0)	0 (0)
Vomiting (%)	0 (0)	0 (0)	0 (0)
Total PONV	4 (10)	0 (0)	0 (0)
Nausea score	1 ±0.2	0	0
12–24 h:			
Nausea (%)	0 (0)	0 (0)	0 (0)

anesthesia and surgery as well as anesthetic drugs used (including intraoperative meperidine) were also similar in all groups. Observed that the mono therapy group required significantly more rescue antiemetic doses than the combined treatment group, increasing the cost of the postoperative emesis treatment. The combination therapy of prophylactic antiemetics achieved greater effectiveness with similar drug cost compared to monotherapy. The study did not reveal any significant difference between the three groups regarding their safety profile. The 1.25 mg droperidol dose neither increased sedation nor other major or minor medication-related side effects.

LIMITATIONS: Lower doses of droperidol (0.625 mg) was not investigated during this study and only used doses of 1.25 mg of droperidol. Excluded patients identified as high risk for PONV according to their medical history. Therefore, further investigation is needed to confirm and expand our results in this population sample.

CONCLUSION: Combination therapy with droperidol and ondansetron is more effective in preventing PONV following elective laparoscopic cholecystectomy than monotherapy with each agent alone, without increasing the cost or the major and minor medication-related side effects, a fact that makes it an effective and safe pretreatment strategy.

Vomiting (%)	0 (0)	0 (0)	0 (0)
Total PONV	0 (0)	0 (0)	0 (0)
Nausea score	0	0	0

*p < 0.01 D + O vs. D
†p < 0.01 D + O vs. O
§p < 0.05 D + O vs. O
‡p < 0.05 O vs. D; nausea score
≠p < 0.05 D + O vs. O.

Table 2: Number of patients who required rescue antiemetic medication (single dose of 4 mg ondansetron) in post-anesthetic care unit (PACU) and ward.

Time after surgery	Group D (*n* = 40)	Group O (*n* = 40)	Group D+O (*n* = 47)
PACU (0–60 min):			
0 mg (%)	19 (47.5)	25 (62.5)	43 (91.5)*†
4 mg (%)	21 (52.5)	15 (37.5)	4 (8.5)*†
Ward (1–24 h):			
0 mg (%)	17 (42.5)	20 (50)	37 (78.7)*‡
4 mg (%)	23 (57.5)	20 (50)	10 (21.3)*‡

*p < 0.01 D + O vs. D
†p < 0.01 D + O vs. O
‡p < 0.05 D + O vs. O.

Secondary Outcomes:

- No significant differences among the three groups regarding total antiemetic cost analyses
  - Group D: €9.21 ±4.14, group O: €8.62 ±3.32, group D + O: €10.12 ±2.13, p > 0.05
- Statistically significant difference between group D + O vs. groups D and O regarding total
  - Median, minimum-maximum range: €0.0, 0.0–4.6 for group D + O and €4.6, 0.0–9.2 for groups D and O, p < 0.01
- Number of patients experiencing minor side effects during the 24-hour postoperative period did not differ significantly
  - headache, dizziness and pruritus
- No statistically significant differences between groups regarding sedation, and no major adverse effects
  - 2 patients of group O and 1 patient of group D + O reported a mild headache
  - Group D 1 patient reported lightheadedness and 1 showed anxiety

			• Nausea scores were statistical significance only between group O and D + O at 3 h ($p < 0.05$) • Nausea scores were statistical significance only between group O and D + O at 3 h ($p < 0.05$)	
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE) High ⊕⊕⊕⊕, Moderate ⊕⊕⊕□, Low ⊕⊕□□, or Very Low ⊕□□□**
Author: Apfel et al., 2004 Title: A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting Comparator: 4 mg of ondansetron or no ondansetron; 4 mg of dexamethasone or no dexamethasone; 1.25 mg of droperidol or no droperidol; propofol or a volatile anesthetic; nitrogen or nitrous oxide; and remifentanil or fentanyl	Randomized, controlled trial of factorial design (n=5161)	Inclusion: All the patients had a risk of postoperative nausea and vomiting that exceeded 40 percent, according to a simplified risk score, based on the presence of at least two of the following risk factors: female sex, nonsmoker status, previous history of postoperative nausea and vomiting or motion sickness, and anticipated use of postoperative opioids. Exclusion: Patients who were contraindicated to any of the study drugs, those who had taken emetogenic or antiemetic drugs within the 24 hours before surgery, those who were expected to require postoperative mechanical ventilation, and those who were pregnant or lactating.	Primary Endpoint: The incidence of any of the following during the first 24 postoperative hours • Nausea • Emetic episodes (retching or vomiting) • Both (i.e., postoperative nausea and vomiting) Results: • 1731 patients (34%) had PONV • 59% patients who were given volatile anesthesia, nitrous oxide, fentanyl, and no antiemetics, 26 of 44 of these patients had N/V • 17% among patients who received propofol, nitrogen, remifentanil, ondansetron, dexamethasone, and droperidol, 17 of 102 of these patients had N/V • Nausea occurred in 1617 patients (31%) and vomiting in 734 (14%) • Bivariate analyses: each antiemetic reduced the incidence of PONV by about 26%, propofol reduced it by about 19%, and nitrogen reduced it by about 12% (Table 3) Table 3: Risk of Postoperative Nausea and Vomiting According to Patients' Randomly Assigned Interventions. **Intervention** | **Received Intervention: Yes** | **Received Intervention: No** | **Percent Relative Risk (95% CI)** | **P-value** **No. with PONV/total no. (%)** **Ondansetron (vs. no ondansetron)** | 735/2576 (28.5) | 996/2585 (38.5) | -26.0 (-31.5 to -19.9 | <0.001 **Dexamethasone (vs. no** | 739/3596 (28.5) | 992/2565 (38.7) | -26.4 (-31.9 to -20.4) | <0.001	**GRADE:** A **QUALITY OF EVIDENCE (GRADE):** High ⊕⊕⊕⊕ **ASSESSMENT:** Low risk **STRENGTHS:** The large enrollment and the factorial design allowed simultaneous evaluation of the antiemetic efficacy of three antiemetic interventions and three anesthetic interventions and of all possible combinations of two or three interventions. There were no significant interactions among the antiemetic interventions, among the anesthetic interventions, or among the antiemetics and the anesthetics. Used low-dose droperidol, 1.25 mg, and did not report any significant adverse drug events. **LIMITATIONS:** The resulting data suggest that antiemetics with different mechanisms of action have additive (rather than synergistic) effects on the incidence of postoperative nausea and vomiting. The study only reported using 1.25 mg of droperidol and not any doses less like 0.625 mg. **CONCLUSION:** Ondansetron, dexamethasone, and droperidol each reduced the risk of postoperative nausea and vomiting by about

			dexamethasone)			
			Droperidol (vs. no droperidol)	742/2573 (28.8)	989/2588 (38.2)	-24.5 (-30.3 to -18.4)	<0.001
			Propofol (vs. no propofol)	1066/3427 (31.1)	665/1734 (38.4)	-18.9 (25.0 to -12.3)	<0.001
			Nitrogen as carrier gas (vs. nitrous oxide)	668/2146 (31.1)	755/2131 (35.4)	-12.1 (-19.3 to -4.3)	0.003
			Remifentanil (vs. fentanyl)	827/2386 (34.7)	792/2403 (33.0)	-5.2 (-2.9 to 13.8)	0.21

Safety: the following were similar between antiemetics
- Rates of hypotension
- Use of intraoperative vasoconstrictors
- Shivering events

26%. In addition, they report that propofol and nitrogen reduced the risk of postoperative nausea and vomiting by 19% and 12%, respectively. Since antiemetics have similar efficacy in the prevention of postoperative nausea and vomiting and since they act independently, according to the results of the current study, we think that the combination of dexamethasone and droperidol is a more favorable and cheaper option than other combinations of antiemetic interventions evaluated in this study for the prevention of postoperative nausea and vomiting.

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or Very Low** ⊕□□□

Author: Fortney et al. 1998
 	
Title: A Comparison of the Efficacy, Safety, and Patient Satisfaction of Ondansetron Versus Droperidol as Antiemetics for Elective Outpatient Surgical Procedures
	Two identically designed, randomized, double-blind, placebo-controlled, multicenter studies were performed in 50 institutions in North America (n=2,061)	Inclusion: American Society of Anesthesiology (ASA) physical status I or II, between the ages of 18 and 65 years old, history of motion sickness or PONV after general anesthesia and scheduled for general anesthesia for outpatient procedures planned to last no more than 2 hours. Certain procedures that were considered high emetogenic potential (laparoscopic, genitourinary, lower extremity orthopedics, umbilical or ventral herniorrhaphies, partial	Primary Endpoint:
			• Number of complete responses to prophylactic treatment
			  ○ Definition: No emetic episodes, no requirement for rescue antiemetic medications
			
			Secondary Endpoint:
			• Percentage of patients requiring at least one rescue medication
			
			Results:
			Primary outcomes:
			• Complete response in the first 2-hour postoperatively was significantly higher in the ondansetron and droperidol groups compared to the placebo group (P<0.05) (Table 4)
			  ○ Ondansetron 4 mg and droperidol 0.625 mg groups were similar (62% and 63%, respectively)
			  ○ Droperidol 1.25 mg group (69%, P<0.05) was significantly greater (Table 4)
				GRADE: B
				
				ASSESSMENT: Uncertain risk
				
				QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□
				
				STRENGTHS: Strengths of this study provided evidence to a large population and variety of procedures that had high emetogenic potential. This studied used different doses of droperidol at low-doses and finding no significant adverse events.
				No significant differences between ondansetron and droperidol (either dose) for emesis prevention during the 24 h postoperative period; satisfaction scores did not differ significantly among antiemetic treatment groups

Comparator: Ondansetron 4 mg IV; droperidol 0.625 mg IV; droperidol 1.25 mg IV; placebo (saline) injection

mastectomies, or lumpectomies) were limited to this study.

Exclusion: Major organ disease, ASA physical status II or greater, weight more than 100% over ideal, pregnancy, breast feeding, history of alcohol or drug abuse, receipt of an investigational drug within 30 days of study, receipt of an agent with antiemetic properties within 24 hour of the study and known hypersensitivity to 5-hydroxytryptamine type 3 antagonist

- Complete response in 24-h period was significantly greater in the treatment groups vs placebo group (P<0.05)
  - No significant difference between the ondansetron and droperidol groups
- Droperidol 1.25 mg group was significantly greater in having no nausea than the ondansetron group (43% vs. 29% respectively) (Table 4)

Table 4. Incidence of Complete Response, Absence of Nausea, Receipt of Rescue Medications, and Hospital Admissions for PONV.

	Placebo	Droperidol 0.625 mg	Droperidol 1.25 mg	Ondansetron 4 mg
Complete response (0-2h)				
Study 1	121/256 (47)*	153/256 (60)	182/253 (72)*	159/257 (62)
Study 2	115/254 (45)*	167/256 (65)†	166/252 (66)	158/253 (62)
Combined studies	236/510 (46)*	320/512 (63)†	348/505 (69)*†	317/510 (62)†
Complete Response (0-24h)				
Study 1	93/255 (36)*	115/253 (45)	152/252 (60)	133/254 (52)
Study 2	93/253 (37)*	129/256 (50)	128/251 (51)	137/251 (55)
Combined studies	186/508 (36)*	244/509 (48)†	280/503 (56)†‡	270/505 (53)†
Absence of Nausea (0-24h)				
Study 1	67/243 (28)	70/228 (31)	109/242 (45)*	75/239 (31)
Study 2	42/234 (18)*	70/248 (28)	95/238 (40)*	64/236 (27)
Combined studies	109/477 (23)*	140/476 (29)†	204/480 (43)*†‡	139/475 (29)†
Rescue medications				
Combined studies	235/518 (45)*	164/518 (32)†	133/510 (26)*†	174/515 (34)†
Admissions for PONV	7/518	7/518	7/510	3/515

Values are proportion (%)
* P < 0.05 compared with ondansetron group.
† P < 0.05 compared with placebo group.
‡ P < 0.05 compared with droperidol 0.625 group.

Secondary outcome:

- Requirement of at least one rescue antiemetic medication was significantly lower in ondansetron and droperidol group vs placebo (P<0.05) (Table 4)

LIMITATIONS: Type of surgical procedure/general anesthetic techniques were variable and not consistent which allowed difficulty in standardization. Limitation on when the treatment medications were given to the patient postoperatively. Did not follow patients post-24 hours after surgery; therefore, unknown the long term benefits of preventing PONV.

CONCLUSION: The study provided evidence that ondansetron 4 mg, droperidol 0.625 mg, and droperidol 1.25 mg to be superior to placebo for the relief of PONV in a study involving more than 2000 adult outpatients at high risk of PONV. Droperidol 1.25 mg IV was more effective in reducing the incidence of emesis in the first 2 hours postoperatively than either ondansetron 4 mg or droperidol 0.625 mg. Differences among the antiemetic treatment groups were no longer present 24 hours after surgery, whereas all remained more effective than placebo. Droperidol 1.25 mg was also more effective than ondansetron 4 mg or droperidol 0.625 mg in reducing the incidence of nausea for the first 24 hours postoperatively. There was no increased incidence of adverse events in the droperidol groups compared with the ondansetron group. Finally, all three antiemetic treatments were superior to placebo in terms of patient satisfaction with the control of PONV.

			• Ondansetron group required rescue medication more significantly than the droperidol 1.25 mg group (34% vs 26%, P < 0.05) (Table 4)
			• 24 patients were admitted overnight due to persistent PONV
			  ○ 7 in two droperidol groups
			  ○ 3 in the ondansetron group
			
			Safety:
			• Adverse events reported were not significant among the treatment groups
			• Headache was the most frequent neurological complication
			  ○ Incidence was significantly lower in the droperidol groups compared with the ondansetron group
			• Incidence of hypotension, sedation, or agitation/anxiety: No significant differences among the treatment groups	

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE) High ⊕⊕⊕⊕, Moderate ⊕⊕⊕□, Low ⊕⊕□□, or Very Low ⊕□□□**
Author: Isbister GK, et al. 2010 Title: Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study Comparators: Droperidol (10 mg) vs. midazolam (10 mg) vs. droperidol + midazolam (5 + 5 mg)	Double-blinded randomized controlled trial (n=91)	Inclusion: Patients aged 18 years or older who had violent and acute behavioral disturbance and requiring physical restraint and parenteral sedation. Exclusion: Successful verbal de-escalation or de-escalation when confronted by the security team (“show of force”), agreement to oral or IV sedation, other sedative medication already administered or patient did not remain in the ED (absconded, escorted off premises by police), and acute seizures/ postictal	Primary Endpoint: • Duration of violent and acute behavioral disturbance ○ Definition: Time security staff was required Secondary Endpoint: • Time until additional sedation was administered • Reduction in the AMSS by 3 points or to a score of 0 or less 20 minutes • Injuries to the patient or staff • Further calls to security for assistance • Any drug-related adverse effect • Abnormal QT interval Results: • 91 patient presentations, 33 received droperidol, 29 received midazolam, and 29 received the combination Primary outcome: • Droperidol had a median duration of violent and acute behavioral disturbance at 20 minutes (IQR 11 to 37 minutes) • Midazolam had a median duration of 24 minutes (IQR 13 to 35 minutes)	**GRADE:** B **QUALITY OF EVIDENCE (GRADE):** Moderate **ASSESSMENT:** Low risk **STRENGTHS:** Similar times to adequate sedation between droperidol and midazolam; more adverse events with midazolam. Additional sedation was required for the midazolam group vs the droperidol group that showed a higher HR in the midazolam group vs droperidol. Midazolam may cause more adverse effects on oversedation and no evidence of QT prolongation significant enough to associated with droperidol. **LIMITATIONS:** Patients who are intoxicated with alcohol or other medications may be more likely to become over sedated. Therefore, patient population would limit the consistency of the adverse events.

- Combination had a median duration of 25 minutes (IQR 15 to 38 minutes)
  Not significantly different (P=0.66)

Secondary outcomes:

- Additional sedation required: (Table 5)
  - Droperidol: 11 (33%; 95% CI 19% to 52%)
  - Midazolam: 18 (62%; 95% CI 42% to 79%)
  - Combination: 12 (41%; 95% CI 24% to 61%)
- Hazard ratio for additional sedation
  - Midazolam vs droperidol group: 2.31 (95% CI 1.01 to 4.71)
  - Combination vs droperidol: 1.18 (95% CI 0.46 to 2.50)

Table 5. Secondary outcomes for the 3 groups in the study

	Droperidol		Midazolam		Droperidol/ midazolam	
	No.	**Proportion % (95% CI)**	**No.**	**Proportion % (95% CI)**	**No.**	**Proportion % (95% CI)**
Additional sedation required	11	33 (19–52)	18	62 (42–79)	12	41 (24–61)
Abnormal QT interval	2†	6 (1–23)	2	7 (1–24)	4	14 (5–33)

AMSS, Altered Mental Status Scale.
† Only 31 of the 33 patients had ECG results available.

Safety:

- Drug-related adverse effects were more common in the midazolam group
- All sedative-related adverse effects in the droperidol and combination group occurred after additional sedation was given
  - Including 3 of the 4 immediately after administration of IV benzodiazepines
- An abnormal QT occurred in 2 of 31 (6%; 95% CI 1% to 23%) droperidol patients
  - Not different from the other groups

Another limitation was that the medications in the study were not dosed according to patient weight, which may have contributed to adverse effects in smaller patients or poor effectiveness in larger patients.

CONCLUSION: Intramuscular droperidol and midazolam resulted in a similar duration of violent and acute behavioral disturbance, but more additional sedation was required with midazolam. Midazolam caused more adverse effects because of oversedation, and there was no evidence of QT prolongation associated with droperidol compared with midazolam

Author, title, date Comparator	Study Design, Number of Patients (n)	Study Population	Endpoint(s) Result(s)	Grade Bias Assessment Quality of the Evidence (GRADE) High ⊕⊕⊕⊕, Moderate ⊕⊕⊕□, Low ⊕⊕□□, or Very Low ⊕□□□

Author: Kreisler NS, et al., 2000
 	
Title: Small-Dose Droperidol Effectively Reduces Nausea in a General Surgical Adult Patient Population
 	
Comparators: Droperidol 0.625 mg IV vs Normal Saline (NS, placebo)
	Prospective randomized, double-blind, placebo-controlled trial (n=150)	Inclusion: Patients undergoing general anesthesia.
		
		Exclusion: Less than 18 years old, pregnancy, allergy to any of the study drugs, routine use of antiemetics and surgical procedures that were intracranial and cardiac procedures.
			Primary Endpoint:
			• Occurrence of N/V in the PACU when comparing 0.625 mg of droperidol IV or an equal volume of NS 30 mins before emergence from general anesthesia
			• If PONV occurred in the PACU, patients were further randomized to receive droperidol 0.625 mg IV, ondansetron 4 mg IV, or promethazine 12.5 mg IV
			• Need for further rescue medications was also included
			
			Secondary Endpoint:
			• The occurrence of side effects when comparing 0.625 mg of droperidol IV or an equal volume of NS 30 mins before emergence from general anesthesia
			
			Results:
			• 150 patients were enrolled in the study where 74 patients received droperidol pretreatment, and 76 patients received the placebo.
			
			Primary outcome:
			• Number of nausea free patients was significantly greater in the pretreated group (P<0.001), than the placebo group (p=0.008)
			• Number of patients who experience PONV in the PACU was significantly decreased in the droperidol group
			  ○ 5/74 patients (6.8%) in the droperidol group
			  ○ 31/76 (40.8%) in the placebo group (P<0.001)
			  ○ Number needed to treat (NNT) was 2.9
			• Patients who experienced PONV (n=31) and required rescue treatment received:
			  ○ Ondansetron (n=7)
			  ○ Promethazine (n=14)
			  ○ Droperidol (n=10)
			• PONV occurrence for each rescue medication
			  ○ Ondansetron: 2/7 (28.6%)
			  ○ Promethazine: 3/14 (21.4%)
			  ○ Droperidol: 1/10 (10%)
				GRADE: B
				
				ASSESSMENT: Uncertain risk of bias
				
				QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□
				
				STRENGTHS: Although the trend was for droperidol to be associated with fewer request for a second antiemetic after breakthrough PONV, the statistical power was insufficient to reach significance (P=0.613) could be considered a minor strength of the study (Figure 3). Used low-dose droperidol and found it to be efficacious and safe in patients for prophylactic PONV.
				
				LIMITATIONS: Potential bias due to patients requiring more antiemetic medications, the choice of medication was directed by the PACU physician where they were unblinded.
				
				CONCLUSION: Administration of droperidol, 0.625 mg IV, is safe and effective in reducing PONV**.** An additional dose of droperidol, ondansetron, and promethazine were equally effective in treating established PONV, without significant differences in side effects.

Secondary outcome:

- No reports of side effects when comparing 0.625 mg of droperidol IV or an equal volume of NS
- Side effects of ondansetron, promethazine, and droperidol when given as a rescue medication for PONV were not statistically significant (Table 6)

Table 6. Side effects of ondansetron, promethazine, and droperidol when given as a rescue medication for PONV.

	Ondansetron	Promethazine	Droperidol	P value
Patients	7	14	10	
PONV within 24 hours (%)	3(43)	3 (21)	4 (40)	0.50
Dizziness	1 (14)	1 (7)	2 (20)	0.64
Headache	3 (42)	2 (14)	2 (20)	0.33
Blurred vision	1 (14)	0 (0)	0 (0)	0.17
Dysphoria	0 (0)	0 (0)	1 (10)	0.39
Dry mouth	4 (57)	9 (64)	6 (60)	0.95

Safety:

- Droperidol provided to be safe and effective in reducing PONV
- There were no reports on side effects of extrapyramidal symptoms or restlessness of any of the groups

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or Very Low** ⊕□□□
Author: Lo et al., 2005 Title: Morphine sparing with droperidol in patient-controlled analgesia (PCA)	Randomized, double-blind clinical study (n=179)	Inclusion: Female patients who were scheduled for abdominal hysterectomy surgery. Exclusion: (1) refusal to provide informed consent; (2) known allergy to butyrophenones and/or opioids; (3) ingestion of	Primary Endpoint: • Pain intensity at rest or on movement and relative sedation score were evaluated and recorded at 6, 12, 24, 48, and 72 hours after surgery Secondary Endpoint: • Related side effects were also evaluated and recorded on postoperative days 1, 2, and 3	**GRADE:** B **QUALITY OF EVIDENCE (GRADE):** High ⊕⊕⊕⊕ **ASSESSMENT:** Low risk **STRENGTHS:** Results show that coadministration of droperidol 50 mcg and morphine 1 mg on demand for PCA decreases postoperative pain

Comparator: PCA with 1 mg morphine and 50 mcg of droperidol on demand vs PCA with 4-hour limit of 30 mg of morphine

antiemetic, antihistamine, and/or opioid medication within 24 hours of anesthesia; (4) known history of heart, pulmonary, hepatic, or renal disease; and (5) suspected or known pregnancy.

Results:

- Morphine use during postoperative 72-h period: significantly lower for the droperidol group than the control group (33.9 ± 9.8 and 54.9 ± 12.1 mg, respectively)
- Pain intensity levels:
  - at 48-h (pain intensity on movement: 3.9 ± 1.2 vs 4.3 ± 0.9, respectively; P = .049)
  - at 72-h (pain intensity on movement: 3.0 ± 1.1 vs 3.6 ± 0.5, respectively; P = .003; pain intensity at rest: 1.3 ± 1.0 vs 1.6 ± 0.7, respectively; P = .033) subsequent to surgery (Table 7)
- Control subjects demonstrated a greater frequency of postoperative nausea and vomiting than did their droperidol counterparts on postoperative day 1

Table 7. Pain and sedation scores at postoperative 48, and 72 hours in patients receiving PCA morphine containing droperidol (droperidol group) or not (control group).

	Parameter	Droperidol	Control	P
48 h	VRSC	3.9 ± 1.2	4.3 ± 0.9	0.049
	VRSR	2.1 ± 1.1	2.3 ± 0.8	0.312
72 h	VRSC	3.0 ± 1.1	3.6 ± 0.5	0.003
	VRSR	1.3 ± 1.0	1.6 ± 0.7	0.033

Values are presented as mean ± SD. VRSC indicates verbal rating score during cough or movement; VRSR, verbal rating score at rest.

Table 8. Morphine consumption (mg) at indicated time intervals in patients receiving PCA morphine containing droperidol (droperidol group) or not (control group)

Time interval (h)	Droperidol group	Control group	*P*
0-6	4.1 ± 1.5	7.0 ± 1.2	.011
6-12	3.3 ± 1.2	4.9 ± 1.3	.039
12-24	5.6 ± 2.2	8.8 ± 2.5	<.001
24-48	11.4 ± 3.5	17.8 ± 3.9	<.001
48-72	9.2 ± 3.0	16.4 ± 3.6	<.001

Safety profile:

- Occurrence of related side effects such as nausea, vomiting, pruritus, and/or extrapyramidal symptoms presented

Table 9. Frequency of related side effects on postoperative days 1, 2, and 3 in patients receiving PCA morphine containing droperidol (droperidol group) or not (control group)

	Droperidol group (n=90)	Control group (n=89)	*P*

intensity, morphine consumption, and frequency of PONV.

LIMITATIONS: Patient population studied was female who undergone abdominal hysterectomy surgery.

CONCLUSION: Coadministration of 50 mcg droperidol and 1 mg morphine on demand via PCA provides a morphine-sparing effect and reduces the frequency of postoperative nausea and vomiting.

			Day 1	Nausea	14 (16)	27 (30)	0.017*
				Vomiting	9 (10)	20 (22)	0.024*
				Pruritis	1 (1)	1 (1)	1.000
				Extrapyramidal symptoms	0 (0)	0 (0)	-
			Day 2	Nausea	4 (5)	11 (10)	0.124
				Vomiting	3 (3)	8 (7)	0.200
				Pruritis	0 (0)	0 (0)	-
				Extrapyramidal symptoms	0 (0)	0 (0)	-
			Day 3	Nausea	0 (0)	0 (0)	-
				Vomiting	0 (0)	0 (0)	-
				Pruritis	0 (0)	0 (0)	-
				Extrapyramidal symptoms	0 (0)	0 (0)	-

Values are presented as number (proportion). * P < 0.05.

Author, title, date	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□

Author: Macht et al., 2014
 	
Title: Comparison of droperidol and haloperidol for use by paramedics: assessment of safety and effectiveness
 	
Summary: This study reviewed agitated patients between 2007 and 2010 who received either haloperidol and droperidol in the prehospital
	Before-after quasi-experiment (n=532; n=314 in haloperidol, n=218 in droperidol)	Inclusion: Identified prehospital patients in transport to one of the study hospitals who had received haloperidol or droperidol	Primary Endpoint:
			• Median changes in QTc interval after administration of droperidol for:
			  ○ Agitation
			  ○ Intractable vomiting
			  ○ Need for repeat sedation within 30-minutes of arrival of the hospital
			
			Secondary Endpoint:
			• Observed emergency department complications in patients receiving prehospital:
			  ○ Droperidol
			  ○ Haloperidol
			
			Results:
			• The Denver Health Paramedic Division responded to 190,292 calls
			  ○ 116,674 [61%] while haloperidol was available
			  ○ 100,645 [39%] when droperidol was available
			• Of the responded calls, 154,764 patients were transported
			  ○ 100,645 [65%] while haloperidol was available
				GRADE: B
				
				ASSESSMENT: Uncertain risk
				
				QUALITY OF EVIDENCE (GRADE): Low ⊕⊕□□
				
				STRENGTHS: Increased inclusion compared to randomized-control trials due to population-level analysis vs individual-level analysis. Methods used to combine the findings of studies were appropriate.
				
				LIMITATIONS: No randomization of patients. Uncertain risk for potential reporting bias.
				
				CONCLUSION: In this cohort of agitated patients treated with haloperidol or droperidol in the prehospital setting, there was no significant difference in QTc prolongation, adverse events, or need for repeat sedation between haloperidol and droperidol. There was a trend

setting. They measured ED ECGs when available to determine QTc prolongation and identified if either agent was safe and effective.

- 54,119 [35%] while droperidol was available
- Final study population
  - 314 patients who received prehospital haloperidol
  - 218 patients who received prehospital droperidol.
    - 11 patients received droperidol 1.25 mg IV or IM as an anti-emetic.
- Mean haloperidol dose: 7.9 mg (median 10 mg, range 4–20 mg)
- Mean droperidol dose: 2.9 mg (median 2.5 mg, range 1.25–10 mg)

	Droperidol (n=166) *N* (%)	**Haloperidol (n=78) *N* (%)**	**Difference (95% CI)**
Median QTc interval in ms (range, IQR)	453 (398–542, 437–469)	448 (386–542, 426–467)	5 ms (−10–6 ms)
QTc 450-474 ms	59 (36)	23 (29)	6% (−6–19%)
QTc 475-499 ms	27 (16)	9 (12)	5% (−4–14%)
QTc >500 ms	5 (3)	3 (2)	1% (−6–4%)

	Droperidol (n=218) *N* (%)	**Haloperidol (n=314) *N* (%)**	**Difference (95% CI)**
SBP <90 mmHg	6 (3)	13 (4)	1.3% (−1.7–4.5%)
Seizure	0 (0)	0 (0)	0 (−0.01–1.2%)
Anti-arrhythmic	1 (0.5)	5 (2)	1.1% (−0.1–2.7%)
Cardioversion/defibrillation	0 (0)	0 (0)	0 (−0.01–1.2%)
BVM	4 (2)	12 (4)	1.9% (−1.0–4.8%)
Intubation	4 (2)	12 (4)	1.9% (−1.0–4.8%)
Cardiopulmonary arrest	1 (0.4)	0 (0)	−0.5% (−1.3–0.04%)
Expired in hospital	0 (0)	0 (0)	0 (−0.01–1.2%)

Safety:

- No seizures, no uses of cardioversion or defibrillation, and no deaths
- One cardiac arrest in the droperidol group (0.4% of the droperidol group, absolute difference from haloperidol group 0.5%, 95% CI: −0.04–1.3%)

toward fewer adverse events and less need for repeat sedation in the droperidol group. Further study with larger patient groups is needed to better define the safest and most effective method to sedate agitated patients in the prehospital setting.

<table>
<tr><td></td><td></td><td></td><td>

This cardiopulmonary arrest immediately followed a struggle with staff while the patient was combative
Patient had return of spontaneous circulation after 1 minute of CPR (before an initial cardiac arrest rhythm was obtained).
Post-arrest QTc was 481 ms; there were no other abnormal features of the ECG
Patient was discharged from the hospital neurologically intact

</td><td></td></tr>
<tr><td>Author, title, date
Comparator</td><td>Study Design, Number of Patients (n)</td><td>Study Population</td><td>Endpoint(s)
Result(s)</td><td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td></tr>
<tr><td><u>Author</u>: Martel et al., 2021

<u>Title</u>:
Randomized Double-blind Trail of Intramuscular Droperidol, Ziprasidone, and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department

<u>Comparator</u>:
Droperidol 5 mg vs ziprasidone 10 – 20 mg vs lorazepam 2 mg</td><td>Prospective randomized double-blind trial
(n=115)</td><td><u>Inclusion</u>: Emergency department patients aged ≥ 18 years old were eligible for inclusion if the treating physician determined they needed parenteral sedation for acute agitation
(July 2004 through March 2005)</td><td><u>Primary Endpoint:</u>
• Proportion of patients adequately sedated at 15 minutes
○ Alerted Mental Status Scale (AMSS ≤ 0)
<u>Secondary Endpoint</u>:
• Need for additional sedating medication
• ED length of stay
• Respiratory depression

<u>Results:</u>
• Adequate sedation at 15 minutes: (Table 12)
○ Droperidol was effective in 16 of 25 (64%) patients
○ 10 mg ziprasidone was effective in 7 of 28 (25%)
○ 20 mg ziprasidone was effective in 11 of 31 (35%)
○ Lorazepam was effective in 9 of 31 (29%)

Table 12. Outcomes
<table>
<tr><th>AMSS score (min)</th><th>Droperidol (n = 25)</th><th>Ziprasidone 10 mg (n = 28)</th><th>Ziprasidone 20 mg (n = 31)</th><th>Lorazepam (n = 31)</th></tr>
<tr><td colspan="5">Proportion adequately sedated, No. (%)</td></tr>
<tr><td>15 min</td><td>16 (64)</td><td>7 (25)</td><td>11 (35)</td><td>9 (29)</td></tr>
<tr><td colspan="5">Additional sedative medications, No. (%)</td></tr>
<tr><td>Entire encounter</td><td>5 (20)</td><td>7 (25)</td><td>5 (16)</td><td>12 (39)</td></tr>
<tr><td colspan="5">Time in the ED (min), median (IQR) - min</td></tr>
<tr><td>Total time in the ED</td><td>563 (477-615)</td><td>540 (438-720)</td><td>551 (455-640)</td><td>611 (439-782)</td></tr>
<tr><td colspan="5">Respiratory outcomes</td></tr>
</table>
</td><td>GRADE: B

SELECTION: Possible useful

QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□

STRENGTH: IM droperidol to be superior to IM lorazepam or IM ziprasidone at two doses for the treatment of acute undifferentiated agitation in the ED. A greater proportion of patients were adequately sedated with droperidol compared to either lorazepam or ziprasidone at both 15 and 30 minutes after injection. In addition, droperidol appears to have a safety advantage as fewer patients receiving droperidol had evidence of respiratory depression.

LIMITATIONS: Data was collected in 2005; therefore, because of the aged data, it is limited to the emergence of novel psychoactive substances, such as “K2,” “spice,” and “bath salts.” This trial’s data may not apply to patients with agitation secondary to acute decompensation of mental illness, drug intoxication, or underlying medical illness.</td></tr>
</table>

Respiratory depression	3 (12)	10 (36)	12 (39)	15 (48)

Safety:
- QTc durations were similar in all groups (p = 0.52)

CONCLUSION: Droperidol was more effective than lorazepam or either dose of ziprasidone for the treatment of acute agitation in the ED and caused fewer episodes of respiratory depression.

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE) High ⊕⊕⊕⊕, Moderate ⊕⊕⊕□, Low ⊕⊕□□, or Very Low ⊕□□□**
Author: Yap et al., 2017 Title: Intravenous midazolam-droperidol combination, droperidol or olanzapine monotherapy for methamphetamine-related acute agitation: subgroup analysis of a randomized controlled trial Comparator: Droperidol (10mg) vs. olanzapine (10 mg) vs. droperidol + midazolam (5 + 5mg)	Multi-center, randomized, double-blind, controlled, clinical trial, subgroup analysis (n=92) October 2014 and September 2015	Inclusion: Patients aged 18-65 years requiring intravenous medication sedation for acute agitation. A subgroup of 92 methamphetamine-affected patient. Patients were identified by self-reporting of methamphetamine use or from collateral reports from accompanying individuals	Primary Endpoint: • Number of patients sedated adequately at 10 minutes or initial dose definition: ○ A score ≤2 based on a six-point, validated acute arousal scale ○ 5 = highly aroused, violent towards self, others or property) ○ 4 = highly aroused and possibly distressed or fearful; 3 = moderately aroused, agitated, more vocal, unreasonable or hostile ○ 2 = mildly aroused, pacing, willing to talk reasonably ○ 1 = settled, minimal agitation; 0 = asleep) Secondary Endpoint: • Time to adequate sedation • Need for additional doses • Open-label sedative medication to achieve adequate sedation • QTc interval • Adverse events Results: • 73/92 patients required mechanical restraint for a median duration of 2 hours • Security assistance was essential in all these cases • A median duration of 33 (23-55) minutes of security staff time was required until the behavioral control was achieved Primary outcome:	**GRADE:** B **ASSESSMENT:** Uncertain risk **QUALITY OF EVIDENCE (GRADE)**: Moderate ⊕⊕⊕□ **STRENGTHS:** Midazolam–droperidol combination resulted in faster time to adequate sedation than either olanzapine or droperidol monotherapy. Adverse events were similar between all three groups. **LIMITATIONS:** Respiratory events were slightly more common in the midazolam-droperidol group. No baseline ECG in patients, only ECG monitoring 30 minutes after administration, which is not following the droperidol's black box warning recommendation. Main limitation of this study is that it is a substudy of a larger trial. Overall, this has reduced power to detect an overall treatment effect. **CONCLUSION:** This study demonstrates that the intravenous midazolam–droperidol combination is superior to either intravenous droperidol or olanzapine monotherapy for the management of methamphetamine-related acute agitation in the ED. These findings contribute to the limited published evidence in an area that consumes

- More than one-third more patients in the midazolam-droperidol group were sedated adequately compared to the droperidol and olanzapine groups
- The median time to sedation for the midazolam-droperidol group was significantly shorter than both the droperidol and olanzapine groups
- 45 patients were sedated adequately with the initial dose of study medications

Table 13. Proportion of patients sedated at 10 mins after first dose administration and median times to adequate sedation: (was there any info in this study about methamphetamine likelihood to increase Qtc?)

	M+D (*n*=34)	**D (*n* = 30)**	**O (*n* = 28)**	**M+D vs D OR, 95%**	**M+D vs O OR, 95%**
At 10 min	29 (85.3)	14 (46.7)	14 (50.0)	6.63 (2.02–21.78)	5.80 (1.74–19.33)

Secondary outcome:

- 26 of the 45 patients who were sedated adequately had been administered the midazolam 5 mg-droperidol 5 mg combination
- 13 of the 92 patients who required open-label sedative medications, only one patient was from the midazolam-droperidol group

Safety:

- The most common AE was oxygen desaturation, and all cases were resolved within a minute without adverse clinical outcomes.

Table 14. The need for additional parenteral sedative medication:

+ Doses, n (%)	**M+D (n=34)**	**D (n=30)**	**O (n=28)**
1 + dose	6 (17.6)	9 (30.0)	8 (28.6)
2 + dose	2 (5.9)	11 (36.7)	11 (39.3)
	M+D (n=34)	**D (n=30)**	**O (n=28)**
Open-label meds, n(%)	1 (2.9)	4 (13.3)	8 (28.6)
Mean dose (SD), mg	6.5 (3) *	15 (4)	15 (4)

*Mean dose for midazolam; all patients in the midazolam–droperidol combination group received a fixed dose of droperidol 5 mg. SD = standard deviation.

Table 15. Reported Adverse events (patients may have experienced more than one event):

considerable emergency services resource. Given that methamphetamine users are usually transported to the ED in an agitated state, more research is needed to develop an evidence-based protocol for management of methamphetamine-related agitation.

OTHER INFORMATION: In the intervention, two additional doses were administered, if required: midazolam 5 mg, droperidol 5 mg, or olanzapine 5 mg. If adequate sedation was not achieved 5 minutes after two additional doses, the doctor could administer additional, open-label, sedative medication(s) at his/her discretion.

	M+D (*n* = 34)	D (*n* = 30)	O (*n* = 28)
# of pts with reported events, *n* (%)	7 (20.6)	2 (6.7)	6 (21.4)
O2 desaturation	5 (14.7)	2 (6.7)	4 (14.3)
Airway obstruction	4 (11.8)	1 (3.3)	0 (0.0)
SBP < 80 mmHg	0 (0.0)	0 (0.0)	1 (3.6)
Prolonged QTc*	2 (5.9)	0 (0.0)	1 (3.6)

*Two patients in the midazolam–droperidol combination group had a QTc (msec) of 501 and 504, respectively. One patient in the olanzapine group had a QTc of 513 msec.

Author, title, date	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⨁⨁⨁⨁, **Moderate** ⨁⨁⨁□, **Low** ⨁⨁□□, **or** **Very Low** ⨁□□□
Author: Hernández-Rodríguez et al., 2022 Title: Prospective real-time evaluation of the QTc interval variation after low-dose droperidol among emergency department patients	Prospective cohort study (n=68)	Inclusion: ≥12 years or older who received low-dose droperidol (≤ 2.5 mg) for indications other than acute behavioral disturbances (i.e., treatment of headache, pain other than headache, nausea, and vomiting) between June 20, 2019, and July 16, 2021 Exclusion: Critically ill patients, altered level of consciousness or agitation, and pregnant patients	Primary Endpoints: • Variation of QTc interval after droperidol administration • Differences between the baseline QTc and the QTc interval at 10, 20, 30, 40 (only for infusion group), and 46 min (only for infusion group) after droperidol initiation. • Number of patients with QTc ≥ 500 ms at any time after droperidol administration Secondary Endpoints: • Clinical adverse events, which were classified as serious or non-serious. Result: Primary outcomes: • Mean maximum delta of QTc interval after droperidol across all 68 patients was +29.9 ms (SD 15) • 12 patients (17.6%) experienced a QTc interval ≥ 500 ms during the observation period after droperidol administration, and 3 patients (4.4%) had a delta QTc ≥ +60 ms Secondary outcomes: • No serious arrhythmias, such as TdP, or deaths among the 68 participants • 13.2% (n = 9) had at least one non-serious adverse event	**Grade**: B-U **ASSESSMENT:** Uncertain risk **QUALITY OF EVIDENCE (GRADE)**: Moderate ⨁⨁⨁□ **STRENGTH:** No patients experienced adverse events, which was consistent to other studies with low-dose droperidol (≤2.5). The QTc interval was measured before and at several time points after droperidol administration which provided us more than 2000 QTc intervals recorded **LIMITATION:** Single-center study at an academic institution with a relatively small sample of patients enrolled. There was a lack of control group which makes the study uncertain if such changes would similarly occur in the absence of droperidol or with other drugs. Droperidol was given at the discretion of ED providers, there is certainly some additional selection bias that could be present due to providers avoiding droperidol in patients at higher risk of having

			• 6 of 41 (14.6%) patients (bolus group) experienced a non-serious adverse event • 3 of 27 (11.1%) of the infusion group experienced non-serious adverse events • Patients who had a non-serious adverse event had higher maximum delta of QTc after droperidol than those without an adverse event (mean + 42.4 ms vs +27.9 ms, mean difference + 14.5 ms, 95% CI +4.29 ms to +24.70 ms, p = 0.009)	cardiac arrhythmias (e.g., those with electrolyte disturbances or underlying cardiac disease). **CONCLUSION:** The QTc intervals slightly increased 10 to 30 min after droperidol administration, but these prolongations were brief, mostly below 500 msec and did not lead to arrhythmias. These data suggest that low-dose droperidol (≤ 2.5 mg) is safe from the cardiac perspective for the use in non-agitated ED patients, and that the yield of continuous cardiac monitoring in this patient population is probably low.
Author, title, date	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□

Author: Calver et al., 2015
 	
Title: The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department
 	
Summary: This observational study determined if 10 mg of droperidol was effective in sedating a patient who has acute behavioral disturbance in the ED
	Prospective, observational study
	(n= 1009)
		Inclusion: Adult patients requiring parenteral sedation for acute behavioral disturbance received droperidol 10 mg.
		
		Exclusion: Patients were excluded if they were willing
		to receive oral medication for sedation or were younger than 18 years.
			Primary Endpoint:
			• The proportion of patients with an abnormal QT interval, defined by the at-risk line on the QT nomogram.
			
			Secondary Endpoint:
			• Effectiveness determined by the time to sedation:
			  ○ Measured on the Sedation Assessment Tool
			• Use of additional sedation
			• Adverse events
			• Injury to staff or patients
			
			Results:
			• 1,009 patients had an ECG performed within 2 hours of droperidol administration
			  ○ Median dose of 10 mg (interquartile range [IQR] 10 to 17.5 mg)
			• 13/1009 patients had an abnormal QT (1.3%; 95% CI 0.7% to 2.3%)
			  ○ 7 of these had another cause attributed for prolonged QT (methadone, escitalopram, amiodarone, or preexisting)
			• In 1,403 patients sedated with a median total dose of droperidol of 10 mg (IQR 10 to 20 mg)
				Grade: B-U
				
				ASSESSMENT: Uncertain risk
				
				QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□
				
				STRENGTH: large sample size, identifying both safety and effectiveness of droperidol for sedation of acute behavioral disturbance in ED
				
				LIMITATION: A limitation of the study was the difficulty obtaining ECGs at the same time for every patient, and many ECGs could not be done within the 2-hour timeframe of administration of droperidol. A second limitation of the study was that in only 1 hospital was the data collection completely consecutive. Another limitation was that not all the demographic and baseline data were available for all patients because the information on the acute behavioral disturbance observation form was incomplete in a small number of cases.

			○ Median time to sedation was 20 minutes (IQR 10 to 30 minutes) and 97% were sedated within 120 min • Additional sedation was required for 435 patients (31.0%; 95% confidence interval 28.6% to 33.5%) • Adverse events occurred in 70 patients (5%) and oversedation without complications in 109 (8%), the latter more common for patients receiving benzodiazepines as additional sedation (16/109 [15%]). • No cases of TdP • Injuries occurred in 34 staff members and 4 patients Safety: • No cases of TdP in the larger cohort of 1,403 patients • Tisk of TdP is less than 0.3% according to the size of cohort • Frequency of abnormal QT intervals was 1.3% (95% CI 0.7% to 2.3%), which was not significantly different to that observed in the control group of patients used to evaluate the QT nomogram, 1.3% (95% CI 0.4% to 3.4%)	**CONCLUSION:** The study supports the use of high-dose droperidol as a safe sedating agent for patients with acute behavioral disturbance in the ED. There is no evidence of increased risk for QT prolongation with the doses used in this study.
Author, title, date	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Cole et al., 2020 Title: The Incidence of QT Prolongation and Tosades des Pointes in Patients Receiving Droperidol in an Urban Emergency Department Summary: This study's objective was to report the	Retrospective observational cohort study	Inclusion: Analysis of any ECG obtained in the ED after the administration of droperidol, regardless of its proximity to the administration of droperidol Exclusion: Critically ill patients with ECGs showing bundle branch blocks or with paced rhythms	Primary Endpoint: • Medication-induced, Bazett corrected QT of ≥ 480 ms Secondary Endpoint: • Critically ill patients with Bazett corrected QT of >480 ms Table 16. ECGs in critically vs non-critically ill patients **Non-critically ill** | **ECG available** | **Analyzed** 15,374 | 2,431 | 2,431 **Critically ill** | **ECG available** | **Analyzed** 11,583 | 1,172 | 396 Results: • Mean QTc in patients with an ECG before droperidol treatment was 421.3 ms (95% confidence interval [CI], 418.0 – 424.6) • The mean QTc in patients with an ECG after droperidol was 421.0 ms (95% CI, 419.5 – 422.5) • In the group with ECGs before and after droperidol treatment	**GRADE**: B-U **ASSESSMENT**: Uncertain Risk **QUALITY OF EVIDENCE (GRADE)**: Moderate ⊕⊕⊕□ **STRENGTHS**: Methods used to combine the findings of studies were appropriate. Many patients receiving droperidol had ECGs available before and/or after administration of droperidol. **LIMITATIONS**: This study was a retrospective chart review. Basett's correction factor over-estimates the risk of the QT interval in

incidence of QT proplongation or torsades de pointe in patients receiving droperidol in the ED by reviewing ECGs in both critically-ill and noncritical patients.			○ Mean QTc was 424.3 ms (95% CI, 419.7 – 428.9) and 427.6 ms (95% CI, 424.3 – 430.9), respectively • The mean ratio of the QTc before to after droperidol treatment was 1.009 (95% CI, 0.99 – 1.02) • 96 critically ill patients had an ECG obtained only before droperidol ○ Mean QTc was 435 ms (95% CI, 428.1–441.9 ms) • In 186 patients an ECG was obtained only after droperidol ○ Mean QTc was 433 ms (95% CI, 427.8 to 438.8 ms) • In 114 patients ECGs were obtained before and after droperidol ○ Mean QTc was 435.7 ms (95% CI, 426.7–444.7 ms) before droperidol ○ Mean QTc was 435.8 ms (95% CI, 427.5–444.1ms) after droperidol • The mean ratio of the QTc before and after droperidol was 1.005 (95% CI, 0.985–1.025) Safety: • One patient of the 16,546 patients enrolled suffered cardiac arrest, deemed unrelated to droperidol ○ Likely cause was due to cardiac arrest provoked by ingestion of an unknown amount of cocaine 11 hours after leaving the ED post administration of a single dose of droperidol • Of the remaining patients ○ 5 experienced ventricular dysrhythmias ○ 4 had bigeminy ○ 1 had torsades de pointe. • Incidence of torsades de pointe: 1/16,546 (0.006%; 95% CI, 0.00015 - 0.03367%)	tachycardic patients, and under-estimates the risk in bradycardic patients. **CONCLUSION**: The incidence of QTc prolongation and torsades de pointes in ED patients receiving droperdiol was found to be extremely rare. The sole case of torsades de pointe was found to have multiple risk factors for dysrhythmias. This study suggests the FDA black box warning to be overstated, and that close monitoring of patients is useful only in high-risk patients, such as those with critical illness and multiple risk factors for torsades de pointe.
Author, title, date	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Faine B, et al., 2012 Title: Treating primary headaches in the	Retrospective case series review (n=73)	Inclusion: Received droperidol between July 1, 2010 to January 8, 2011 identified through electronic medical records identifying patients who	Methods: • Efficacy defined subjectively by the patient (e.g., numerical pain scale from 0 to 10) and/or documented in the medical record by the physician.	**GRADE:** B-U **QUALITY OF EVIDENCE (GRADE):** Low ⊕⊕□□ **ASSESSMENT:** High risk

ED: can droperidol regain its role?
 	
Summary: This retrospective case study determines if droperidol doses less than 2 mg were efficacious in the treatment of primary headaches in the emergency department.
		received low dose (≤2 mg) droperidol for treatment of primary headaches in the emergency department
		
		Exclusion: Patients who received droperidol for any other reason other than treatment of headache were excluded
			• If pain scale was conducted before droperidol administration, a greater than or equal to 50% decrease in the pain score.
			• Adverse effects after the administration of droperidol defined as all new symptoms:
			  ○ Reported by the patient
			  ○ Observed by a healthcare provider
			
			Results:
			• Cumulative droperidol doses ranged from 0.625 to 2 mg with most doses (92%) administered were 1.25 mg or less and the median initial dose was 1.25 mg
			• Six patients (8%) required repeat dosing, of note the median initial dose of those patients was 0.938 mg and the median second dose was 0.625 mg
			• Fifty-three patients (73%) had complete resolution or significant improvement in headache symptoms as documented by the reported decrease in numerical pain scale or by patient care notes in the medical record.
			• Eight patients (11%) had minimal improvement in their headache symptoms; 12 patients (16%) received no relief after administration of droperidol
			• Twenty-three patients had a pain scale recorded pre-administration and post-administration of droperidol. Eighteen patients had a 50% or more decrease in numerical pain scale after the administration of droperidol
			• Of these 18 patients, 2 subjectively described minimal improvement in their headache symptoms, although they reported a 50% or more decrease in numerical pain scale.
			• Of these 23 patients, 5 did not report a 50% or more decrease in their pain scale but subjectively reported that their headache symptoms were resolved or almost completely resolved
			• The median decrease in the numeric pain scale was 5 (range, 1-9)
			• Only 10% received additional medications after they received droperidol to treat their headache
			• Additional medications included metoclopramide, dexamethasone, ondansetron, ketorolac, hydrocodone/acetaminophen, and morphine
				STRENGTHS: This study focused on low dose droperidol.
				
				LIMITATIONS: Observational case-series, determination of efficacy as made based on documentation and extracted by the chart reviewer which could be subjected to bias. As a retrospective study, there was no way to control the interventions. Efficacy results could have been skewed by patients who pain medications although documentation states relief after droperidol. Less than 30% of patients had pain numerical score done before droperidol administration.
				
				CONCLUSION: The use of low-dose droperidol less than or equal to 2 mg for the treatment of primary headaches in the ED is safe and effective.

Author, title, date	**Study Design,**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)**

<table>
<tr><th></th><th>Number of Patients (n)</th><th></th><th></th><th>High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</th></tr>
<tr><td>Author: Gaw et al., 2020

Title: Effectiveness and safety of droperidol in a United States emergency department

Summary: This study determined the mortality within 24 hours of droperidol administration due to the potential of fatal arrhythmias.</td><td>Observational cohort study (n=6353 patient visits at the ED)</td><td>Inclusion: All droperidol administrations from 1/1/2012 through 4/19/2018 at the ED</td><td>Primary Endpoint:
• Mortality within 24 hours

Secondary Endpoint:
• Extrapyramidal symptoms
• Rescue analgesic used

Results: n=6,353
<table><tr><th>Indication</th><th>Received Droperidol</th></tr><tr><td>Pain</td><td>1387 (21.8%)</td></tr><tr><td>Headache</td><td>3622 (57%)</td></tr><tr><td>Sedative</td><td>550 (8.7%)</td></tr><tr><td>Antiemetic</td><td>794 (12.5%)</td></tr></table>
Primary:
• Zero deaths attributable to droperidol administration were recorded within 24 hours among 5784 patients (n=6881 visits).
• One patient died within 24 hours of droperidol administration from respiratory failure unrelated to droperidol administration.
• Noting there was no fatal arrhythmias or QTc prolongation.

Secondary:
• Use of rescue analgesia and opioids.

Table 17. Need for rescue analgesia, n=796 charts
<table><tr><th>Indication</th><th>Number of patients, N (%)</th></tr><tr><td>Headache</td><td>188 (5.2%)</td></tr><tr><td>Pain other than headache</td><td>102 (7.4%)</td></tr><tr><td>Headaches with rescue opioids</td><td>38 (1.1%)</td></tr><tr><td>Pain other than headache with rescue opioids</td><td>75 (5.4%)</td></tr></table>
Table 18. Symptom resolution, n=796 charts
<table><tr><th>Indication</th><th>Resolutions, n (%)</th><th>Total of patients</th></tr><tr><td>Pain</td><td>56 (50.0)</td><td>112</td></tr><tr><td>Headache</td><td>406 (79.5)</td><td>511</td></tr><tr><td>N/V</td><td>65 (56.5)</td><td>115</td></tr><tr><td>Sedation</td><td>28 (48.3)</td><td>58</td></tr></table>
Adverse effects:
• Extrapyramidal symptoms: 796 charts, 2.9% (N=23) of cases had akathisia and resolved with diphenhydramine.</td><td>GRADE: B-U

ASSESSMENT: Uncertain risk of bias

QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□

STRENGTHS:
QT prolongation was rare amount the >6,000 ED visits that received droperidol in this study. Of the 6,353 patient visits, 2,157 (34.0%) had ECG within 6 months including 3.6% (n=77) with QTc≥500 prior to the ED visit.

LIMITATIONS:
This study was conducted at a single site and the data collection was retrospectively. This study is only focused on effectiveness, not efficacy. There was no standardization on droperidol dose or stratification on the doses used. Not all adverse events like akathisia and dystonia were not recorded as a final diagnosis in any of the patients. Other adverse events may not be recorded due to its transient nature and was resolved with either diphenhydramine or benztropine. Around 7.7% of patients did not allow their medical records to be used for research.

CONCLUSION: There were no fatalities attributable to patients who received droperidol in the ED. Less than 8% of the patients with headache or pain needed a rescue analgesic after droperidol administration. Findings suggest droperidol’s effectiveness and safety when used as an analgesic, antiemetic, and/or sedative.</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td>Safety: n=796 charts
<table>
<tr><th>Arrhythmias and QTc prolongation</th><th>N = 6,353 Visits</th></tr>
<tr><th>ECGs</th><th>n (%)</th></tr>
<tr><td>Up to 6 months before droperidol</td><td>2,157 (34.0)</td></tr>
<tr><td>No</td><td>4,196 (66.1)</td></tr>
<tr><td>Yes, with QTc < 500</td><td>2,080 (32.7)</td></tr>
<tr><td>Yes, with QTc ≥ 500</td><td>77 (1.2)</td></tr>
<tr><td>No</td><td>4,679 (73.7)</td></tr>
<tr><td>Yes, with QTc < 500</td><td>1,631 (25.7)</td></tr>
<tr><td>Yes, with QTc ≥ 500</td><td>43 (0.7)</td></tr>
</table></td><td></td></tr>
<tr><td>Author, title, date
Comparator</td><td>Study Design, Number of Patients (n)</td><td>Study Population</td><td>Endpoint(s)
Result(s)</td><td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⨁⨁⨁⨁,
Moderate ⨁⨁⨁◻,
Low ⨁⨁◻◻, or
Very Low ⨁◻◻◻</td></tr>
<tr><td>Author: Meek et al., 2019

Title: Randomized Placebo-controlled Trial of Droperidol and Ondansetron for Adult Emergency Department Patients with Nausea

Comparator: Droperidol 1.25mg IV vs. Ondansetron 8mg IV</td><td>Triple-blind, randomized, controlled trial; superiority trial

(n=215)</td><td>Inclusion: ≥18 years old, with nausea severity at recruitment of ≥4 from any underlying cause. The severity screening used an 11-point verbal rating scale, with 0 being described as no nausea and 10 as the worst nausea imaginable

Exclusion:
1. allergy to ondansetron or droperidol;
2. prior use (previous 4 hours) of an antiemetic drug (including ondansetron, droperidol, metoclopramide, promethazine, chlorpromazine, prochlorperazine, and any steroid medication)
3. too unwell to participate for any reason (e.g.,</td><td>Primary Endpoint:
• Between-group comparisons of the number (percentage) of patients with a measured visual analog scale (VAS) change of –8 mm or more.

Secondary Endpoint:
• Between-group comparisons of mean measured VAS change
• Between-group comparisons of mean percentage VAS change
• Between-group comparisons of the number (percentage) of patients with a percentage VAS change of –20% or more

Other endpoints:
• Between-group comparisons of number (percentage) of patients experiencing the desired treatment effect (this was elicited from direct questioning – “The drug I received had the desired effect for me: Yes or No”)
• Number (percentage) of patients requesting additional antiemetic drugs; and adverse events are reported for each group.
• The most frequently expected events of agitation/sedation (droperidol), dizziness (droperidol), and headache (ondansetron) were specifically assessed.
• The presence and degree of agitation or sedation was rated on the Richmond Agitation-Sedation Scale (RASS) at the time of the 30-minute nausea severity rating by the attending physician (+4 = combative, +3 = very agitated, +2 = agitated,</td><td>GRADE: B-U

ASSESSMENT: Uncertain risk

QUALITY OF EVIDENCE (GRADE): Low ⨁⨁◻◻

STRENGTHS: This study did not demonstrate superiority for either droperidol or ondansetron compared to placebo. Meaning, that droperidol and ondansetron are equivalent in effectiveness in the treatment of adult ED patients with nausea.

LIMITATIONS: Subjective primary endpoint in visualizing if a patient is still nauseated. Antiemetic drugs may not truly provide additional benefit to patients who are nauseated because the treatment would be treating their underlying condition. Calculation was based on “anticipated” symptom improvement rates. The sample may not be representative of all ED patients with nausea. Varied fluid supplementation during the study period may be a confounder to the study.</td></tr>
</table>

		cardiovascular instability or altered mental state); 4. contraindication to a normal saline infusion (e.g., fluid-restricted patients); 5. Parkinson's disease or restless leg syndrome; 6. current use of a dopamine antagonist medication 7. cognitive impairment or language barrier compromising study understanding; 8. pregnant or breastfeeding women; 9. chemotherapy- or radiotherapy-induced nausea	+1 = restless, 0 = alert and calm, –1 = drowsy, –2 = light sedation, –3 = moderate sedation, –4 = deep sedation, –5 = unrousable). • Presence/severity of headache and dizziness were rated on an adjectival scale as none, mild, moderate, or severe. • Any other adverse events of any type were to be noted as free text. Results: n=215 **Study Drugs** / **Number of patients, n (%)** Droperidol: 73 (34) Ondansetron: 71 (33) Placebo: 71 (33) Primary outcome: • Numbers with VAS change of –8 mm or more for droperidol, ondansetron, and placebo were similar, being 55 of 73 (75%, 95% CI = 64%–85%), 57 of 71 (80%, 95% CI = 69%–89%), and 54 of 71 (76%, 95% CI = 64%–85%), respectively (p = 0.75, Pearson chi-square) Table 19. VAS change of –8 mm or more for droperidol, ondansetron, and placebo. **Outcome Measure** / **Individual Treatment Groups**: **Droperidol (*n* = 73)** / **Ondansetron (*n* = 71)** / **Placebo (*n* = 71)** Measured VAS change ≥ –8 mm, *n* (%) [95% CI]: 55 (75%) [64 to 85] / 57 (80%) [69 to 89] / 54 (76%) [64 to 85] Mean measured VAS change, mm [95% CI]: –29 [–36 to –23] / –34 [–41 to –28] / –24 [–29 to –19] % VAS change ≥ 20%, *n* (%) [95% CI]: 54 (74%) [62 to 84] / 53 (75%) [63 to 84] / 52 (73%) [61 to 83] Mean % VAS change, % [95% CI]: –50% [–59 to –40] / –55% [–64 to –46] / –41% [–49 to –33] Experienced desired effect, *n* (%) [95% CI]: 56 (77%) [65 to 86] / 52 (73%) [61 to 83] / 42 (59%) [47 to 71] Table 20. VAS change of –8 mm or more between-group differences. **Outcome Measure** / **Between-group Differences**: **Droperidol –Placebo** / **Ondansetron –Placebo** / **Ondansetron –Droperidol** VAS change ≥ –8 mm, *n* (%) [95% CI]: –1% [–15 to 13] NNT = 99 / 4% [–10 to 18] NNT = 25 / 5% [–9 to 19] NNT = 20 Mean VAS change, mm [95% CI]: 5 [–3 to 13] / 10 [2 to 18] / 5 [–4 to 14]	**CONCLUSION:** For adult ED patients with nausea, superiority was not demonstrated for droperidol or ondansetron over placebo.

			<table><tr><td>% VAS change ≥ 20%, *n* (%) [95% CI]</td><td>1% [–13 to 15] NNT = 99</td><td>2% [–12 to 16] NNT = 50</td><td>–1% [–15 to 13] NNT = 99</td></tr><tr><td>Mean % VAS change, % [95% CI]</td><td>9% [–3 to 21]</td><td>14% [–2 to 26]</td><td>5% [–8 to 18]</td></tr><tr><td>Experienced desired effect, *n* (%) [95% CI]</td><td>18% [3 to 33] NNT = 5</td><td>14% [–1 to 29] NNT = 7</td><td>–4% [–18 to 10] NNT = 5</td></tr></table> Safety: • Additional antiemetic medications were requested by 11 of 73 (15%) in the droperidol group, 16 of 71 (23%) in ondansetron group, and 21 of 71 (30%) in placebo group • Of the 48 who requested extra medication, 43 (90%) had not experienced the desired treatment effect • A reduced level of alertness (moderate sedation, light sedation, or drowsiness) was noted significantly more often in the droperidol group, compared with the ondansetron and placebo group (27/73 [37%, 95% CI = 26%–49%] vs. 9/71 [13%, 95% CI = 6%–23%] and 12/71 [17%, 95% CI = 9%–28%], respectively, p = 0.001 • Restlessness or agitation was noted for four of 73 (5%, 95% CI = 2%–13%), two of 71 (3%, 95% CI = 0%–10%), and two of 71 (3%, 95% CI = 0%–10%), respectively • Headache was reported by 12 of 73 (16%), 13 of 71 (18%), and 20 of 71 (28%), respectively • Dizziness was reported by 11 of 73 (15%), five of 71 (7%), and 11 of 71 (15%), respectively	
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Nuttall et al, 2013 Title: Dose low-dose droperidol increase the risk of polymorphic ventricular	Retrospective study (n = 20,122)	Inclusion: Surgical patients who received a low dose droperidol between March 2007 to February 2011 Exclusion: Patients with no 12-lead electrocardiogram that was crossmatched	Primary Endpoint: • Incidence of polymorphic VT or death Secondary Endpoint: • Polymorphic VT or death for any patients with a previously documented prolonged QTc Results:	**GRADE:** B-U **QUALITY OF EVIDENCE (GRADE):** Moderate ⊕⊕⊕□ **ASSESSMENT:** Low risk

tachycardia or death in the surgical patient? Summary: This study performed a retrospective study to determine if low dose droperidol (0.625 mg) administration was associated with torsade de pointes in the general surgical population.		with the pharmacy database.	• From March 2008 to February 2011, 12 out of 20,122 surgical patients had VT (n = 4; event rate = 2.0 per 10,000, 95% CI 0.5 to 5.1 per 10,000) or died (n = 8; event rate = 4.0 per 10,000, 95% CI 1.7 to 7.8 per 10,000) within 48 h of droperidol administration • There were no patients who clearly developed polymorphic VT or died due to droperidol administration (n = 0; event rate = 0.0 per 10,000, 95% CI 0.0 to 1.8 per 10,000) • All the eight patients who died were on palliative care and died of their disease Safety: • The investigators of this study found 20,122 surgical patients who were exposed to low dose droperidol with no evidence suggesting that it increases the incidence of adverse outcomes.	**STRENGTHS:** All patients included in the final analysis had received droperidol and a 12-lead electrocardiogram. **LIMITATIONS:** The limitations include the inability to capture brief episodes of polymorphic VT with a 12-lead electrocardiogram, the correct diagnosis of the event, and technical issues related to data collection and extraction. **CONCLUSION:** The investigators of this study concluded that the use of low-dose droperidol for the prevention and treatment of nausea and vomiting in the surgical population is safe when combined with discretionary medical judgement.
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or Very Low** ⊕□□□
Author: White et al., 2005 Title: Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study Comparator: Droperidol 0.625	Randomized, double-blind, placebo-controlled study (n = 30)	Inclusion: outpatients undergoing otolaryngologic procedures with a standardized general anesthetic technique Exclusion: Patients with cardiac disease, atrioventricular conduction delays or bundle branch blocks, a history of alcohol or drug abuse within the past 3 months, or morbid obesity. Patients who had taken any antiemetic	Primary Endpoint: • Evaluate the intraoperative and postoperative effects of small dose droperidol (0.625 and 1.25 mg intravenous) on the QT interval when used for antiemetic prophylaxis during general anesthesia Secondary Endpoint: • To assess the effects of low dose droperidol on PONV and adverse clinical cardiovascular outcomes Results: • Average QT interval showed no statistical differences between the treatment groups ○ Droperidol 0.625 mg: 15±40 ms ○ Droperidol 1.25 mg: 22±41 ms	**GRADE:** B-U **ASSESSMENT:** Uncertain risk **QUALITY OF EVIDENCE (GRADE)**: Low ⊕⊕□□ **STRENGTHS**: use of droperidol in the therapeutic dosage range (0.625–1.25 mg intravenous) was associated with clinically significant effects on the electrocardiogram or adverse cardiovascular outcomes. Is this accurate? **LIMITATIONS:** The two-part study included study samples too small to detect rare

<table>
<tr>
<td>mg vs 1.25 mg vs. placebo</td>
<td></td>
<td>medication within 24 h before surgery or were pregnant or experiencing menstrual symptoms were also excluded.</td>
<td>

Saline 12±35 ms

There was however a 14- to 16-ms prolongation with general anesthesia alone but there was no evidence in the peri or postoperative period of a droperidol induced QT prolongation

Table 21. QT intervals for droperidol 0.625 mg vs 1.25 mg vs. placebo
<table>
<tr><th></th><th>Control</th><th>0.625 mg Droperidol</th><th>1.25 mg Droperidol</th></tr>
<tr><td>QT interval before injection, ms</td><td>406 +/- 28</td><td>400 +/- 56</td><td>396 +/- 46</td></tr>
<tr><td>QTc before injection, ms</td><td>439 +/-28</td><td>435 +/-27</td><td>429 +/- 26</td></tr>
<tr><td>QTc at 10 min after injection, ms</td><td>446 +/- 35</td><td>449 +/- 40</td><td>444 +/- 52</td></tr>
<tr><td>QTc =< baseline at 10 min, n (%)</td><td>10 (50)</td><td>6 (30)</td><td>8 (40)</td></tr>
<tr><td>QTc prolongation 0–10% at 10 min, n (%)</td><td>8 (40)</td><td>11 (55)</td><td>10 (50)</td></tr>
<tr><td>QTc prolongation 10–25% at 10 min, n (%)</td><td>2 (10)</td><td>3 (15)</td><td>2 (10)</td></tr>
<tr><td>Mean maximum QTc, ms*</td><td>12 +/- 35</td><td>15 +/- 40</td><td>22 +/- 41</td></tr>
<tr><td>Maximum QTc prolongation, ms</td><td>58</td><td>120</td><td>133</td></tr>
<tr><td>Electrocardiographic rhythm disturbances, n</td><td>0</td><td>0</td><td>0</td></tr>
</table>
<u>Safety:</u>

120 outpatients undergoing otolaryngologic procedures with a standardized general anesthetic technique were enrolled in this study
After anesthetic induction and before the surgical incision, 60 patients were given either saline or 0.625 or 1.25 mg intravenous droperidol in a total volume of 2 ml
A standard electrocardiographic lead II was recorded immediately before and every minute after the injection of the study medication during a 10-min observation period
The QTc (QT interval corrected for heart rate) was evaluated from the recorded electrocardiographic strips
In 60 additional patients, a 12-lead electrocardiogram was obtained before and at specific intervals up to 2 h after surgery to assess the effects of droperidol and general anesthesia on the QTc
Any abnormal heartbeats or arrhythmias during the operation or the subsequent 2-h monitoring interval were also noted

</td>
<td>cardiovascular events. The doses used in this study to examine the effect on QTc interval may not apply to situations where the drug is used for the treatment of PONV.
=
CONCLUSION: This analysis concluded that in the setting leading up to and immediately after surgery there was not a statistically significant increase in QTc interval with the use of small dose droperidol (0.625 mg-1.25 mg) for antiemetic prophylaxis in comparison to saline.</td>
</tr>
</table>

<table>
<tr><th>Author, title, date
Comparator</th><th>Study Design, Number of Patients (n)</th><th>Study Population</th><th>Endpoint(s)
Result(s)</th><th>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</th></tr>
<tr>
<td>Author: Taylor et al., 2017

Title: Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial

Comparator: Droperidol (10mg) vs. olanzapine (10 mg) vs. droperidol + midazolam (5 + 5mg)</td>
<td>Randomized, controlled, double-blind, triple- dummy</td>
<td>Inclusion: age 18-65, required intravenous medication sedation for acute agitation

Exclusion: previously enrolled in the trial, known hypersensitivity or contraindication, had a reversible cause for their agitation</td>
<td>Primary Endpoint:
• Proportion of patients adequately sedated within 10 minutes of the first dose administration

Secondary Endpoint:
• Time to adequate sedation
• Need for re-sedation less than 60 minutes after achieving sedation
• Re-sedation from 60 minutes after sedation until ED discharge
• Sedation medication failure (alternate medications required)
• ECG and QTc interval
• Droperidol adverse events

Results:
Primary Outcome
• Midazolam-droperidol group was more adequately sedated at 10 min vs droperidol or olanzapine group (% differences in proportions 25.0% [95% CI 12.0% to 38.1%] and 25.4% [95% CI 12.7% to 38.3%], respectively)

Table 22. Outcome data
<table>
<tr><th></th><th>Midazolam - droperidol (n=118)</th><th>Droperidol (n=111)</th><th>Olanzapine (n=120)</th></tr>
<tr><td colspan="4">Primary Outcome</td></tr>
<tr><td>Proportion sedated at 10 min. No. (%)</td><td>88 (74.6)</td><td>55 (49.6)</td><td>59 (49.2)</td></tr>
<tr><td colspan="4">Secondary Outcomes</td></tr>
<tr><td>Adequately sedated at 10 min.</td><td></td><td>25% (95% CI 12 – 38.1%)
*Compared to midazolam - droperidol group</td><td>25.4% (95% CI 12.7 – 38.3%)
*Compared to midazolam - droperidol group</td></tr>
<tr><td>Re-sedation < 60 min after</td><td>7 (5.9)</td><td>5 (4.5)</td><td>10 (8.3)</td></tr>
</table>
</td>
<td>GRADE: B-U

ASSESSMENT: Low risk

QUALITY OF EVIDENCE (GRADE): Low ⊕⊕□□

STRENGTHS: Midazolam–droperidol combination resulted in faster time to adequate sedation than either olanzapine or droperidol monotherapy. Adverse events were similar between all three groups. Study design ensured low risk of performance bias. Strong evidence for the use of droperidol with midazolam.

LIMITATIONS: There is a possibility of measurement bias in regards to the sedation scale. However, the study mitigated this potential by utilizing a validated scale, training all staff and ensured blinding of the ED staff. Lastly, patients were enrolled based on patient and staff safety considerations allowing for selection bias.

CONCLUSION: The study concluded that the combination of midazolam-droperidol is superior to either droperidol or olanzapine monotherapy for intravenous sedation of the acutely agitated ED patient based on higher proportions of patients sedated at any point, shorter times to sedation, and lower proportions requiring additional sedatives with the combination regimen.</td>
</tr>
</table>

			<table><tr><td>**Re-sedation > 60 min after**</td><td>26 (22)</td><td>16 (14.4)</td><td>28 (23.3)</td></tr></table> Secondary outcome: • The differences in medians for times to sedation between the midazolam-droperidol and droperidol, and midazolam-droperidol and olanzapine groups were 6 minutes (95% CI 3 to 8 minutes) and 6 minutes (95% CI 3 to 7 minutes), respectively • Fewer patients in the midazolam-droperidol group required additional doses or medications other than additional doses. • No differences between the groups who required re-sedation after initial adequate sedation had been achieved Safety: <table><tr><td></td><td>**Midazolam-droperidol (n=118)**</td><td>**Droperidol (n=111)**</td><td>**Olanzapine (n=120)**</td></tr><tr><td>**Prolong QTc (> 500 ms) No. (%)**</td><td>1 (0.8)</td><td>3 (2.7)</td><td>3 (2.5)</td></tr><tr><td>**Bradycardia (>60 beats/min)**</td><td>0</td><td>2 (1.8)</td><td>5 (4.2)</td></tr></table> • An ECG was obtained within 30 minutes of the first dose for 193 patients (55.3%): midazolam-droperidol 71 (60.2%), droperidol 61 (55.0%), and olanzapine 61 (50.8%) • Median QTc intervals of the 3 groups were similar: 450 ms (range 325 to 501 ms), 442 ms (range 320 to 501 ms), and 445 ms (range 313 to 501 ms), respectively • No patient experienced a cardiac adverse event	
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Tracz et al., 2015 Title: Small doses of droperidol do not present relevant	Randomized double blinded (n=75)	Inclusion: Patients were already due to undergo elective orthopedic surgery, age 18-60, have an American Society of Anesthesiologist grade I or	Primary Endpoint: • Assess effect of small doses of droperidol on: o Cardiac repolarization o QTc interval o Transmural dispersion of repolarization Results:	**Grade:** B-U **SELECTION:** Possible to uncertain usefulness **QUALITY OF EVIDENCE (GRADE)**: Low ⊕⊕□□

<table>
<tr><td>torsadogenic actions: a double-blind, ondansetron-controlled study

Comparator: Droperidol 0.625 mg vs droperidol 1.25 mg vs ondansetron 8 mg</td><td></td><td>II, and a pre-operative QT and QTc less than 440 ms

Exclusion: Patients with abnormal conduction and arrhythmias (including sinus bradycardia/ tachycardia and sinus arrhythmia), treated with QT prolonging drugs, coronary heart disease or heart failure, congenital or acquired heart defects, myocarditis. Pre-operative electrolyte imbalances, or treated with anti-arrhythmic, psychotropic drugs, macrolides or fluoroquinolones.</td><td>• The major finding of this study was that droperidol 1.25 mg, given intravenously, provoked a slightly higher and transient corrected QT interval prolongation without influencing the TDR in men without cardiovascular disorders
• The study also demonstrated that 0.625 mg doses of droperidol produced lower or about equal QT intervals as 8 mg of ondansetron correcting with Bazzett's and Framingham formulas
Table 23. QTc interval of droperidol 0.625 mg vs droperidol 1.25 mg vs ondansetron 8 mg
<table><tr><th></th><th>5 min</th><th>10 min</th><th>15 min</th><th>20 min</th><th>P-value</th></tr><tr><td colspan="6">QTc > 450 ms</td></tr><tr><td>0.625 mg droperidol</td><td>1 (4%)</td><td>1 (4%)</td><td>0</td><td>2 (85)</td><td>0.19</td></tr><tr><td>1.25 mg droperidol</td><td>3 (12%)</td><td>2 (8%)</td><td>2 (8%)</td><td>1</td><td></td></tr><tr><td>8 mg ondansetron</td><td>0</td><td>0</td><td>0</td><td>1 (4%)</td><td></td></tr><tr><td colspan="6">QTc > 480 ms</td></tr><tr><td>0.625 mg droperidol</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0.77</td></tr><tr><td>1.25 mg droperidol</td><td>0</td><td>1 (4%)</td><td>0</td><td>1 (4%)</td><td></td></tr><tr><td>8 mg ondansetron</td><td>0</td><td>1 (4%)</td><td>0</td><td>0</td><td></td></tr></table></td><td>STRENGTHS: Identifying droperidol dosing for QTc prolongation

LIMITATION: No safety data was collected in this study. Patient population consists of only men.

CONCLUSION: Droperidol in lower doses may induce the same QTc prolongation potential as ondansetron.</td></tr>
<tr><td>Author, title, date
Comparator</td><td>Study Design, Number of Patients (n)</td><td>Study Population</td><td>Endpoint(s)
Result(s)</td><td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td></tr>
<tr><td>Author: Chan et al., 2013

Title: Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient:</td><td>Randomized, double blind, placebo-controlled, double-dummy</td><td>Inclusion: Inclusion criteria were aged 18 to 65 years and the need for parenteral drug sedation for acute agitation, as determined by ER provider.

Exclusion: Exclusion criteria were known hypersensitivity or</td><td>Primary Endpoint:
• Time to adequate sedation
• Proportion of patients sedated at specific points

Secondary Endpoint:
• Need for rescue medications
• Adverse events

Results:
<table><tr><th>Variable</th><th>Control</th><th>Droperidol</th><th>Olanzapine</th></tr></table></td><td>GRADE: B-U

ASSESSMENT: Possible to uncertain usefulness

QUALITY OF EVIDENCE (GRADE): Low ⊕⊕□□

STRENGTHS: Droperidol and olanzapine, as adjuncts to titrated midazolam, similarly decrease time to adequate sedation versus midazolam alone. Droperidol and olanzapine</td></tr>
</table>

a multicenter, randomized, double-blind, placebo-controlled clinical trial Comparator: Placebo vs. olanzapine (5 mg) vs. droperidol (5 mg) all as adjuncts to midazolam		contraindication to midazolam, droperidol, or olanzapine; cause of agitation; known pregnancy; and acute alcohol withdrawal. Patients who had recently received (within the previous 12 hours) oral or parenteral sedative drug(s), either as usual medications or out-of-hospital acute agitation treatment were eligible if they met other eligibility criteria.	<table><tr><th></th><th>n=115</th><th>n=112</th><th>n=109</th></tr><tr><td>Time to sedation, mean (SD), min</td><td>67.8 (197.5)</td><td>21.3 (97.1)</td><td>14.0 (33.3)</td></tr><tr><td>Time to sedation, median (IQR), min</td><td>10 (4-25)</td><td>6 (3-10)</td><td>5 (3-10)</td></tr><tr><td>At 5</td><td>31 (27.0)</td><td>40 (35.7)</td><td>39 (35.8)</td></tr><tr><td>At 10</td><td>56 (48.7)</td><td>74 (66.1)</td><td>74 (67.9)</td></tr><tr><td>At 30</td><td>90 (78.3)</td><td>103 (92.0)</td><td>98 (89.9)</td></tr><tr><td>At 60</td><td>100 (87.0)</td><td>106 (94.6)</td><td>104 (95.4)</td></tr></table> Safety: • The administration of intravenous droperidol or olanzapine as a bolus adjunct to intravenous midazolam is efficacious and safe and provides more rapid sedation for acutely agitated patients in the ED compared with intravenous midazolam monotherapy • At the dose administered in this study (5 mg), intravenous droperidol does not appear to affect the QTc interval • Intravenous olanzapine appears safe and effective at the dose administered (5 mg) and in this setting	required less rescue sedation than midazolam alone; adverse events were similar between all three groups. **LIMITATION:** Selection bias may have occurred through physician's preference of which sedative drugs, study neglect and excessive ED activity. **CONCLUSION:** Intravenous droperidol or olanzapine as an adjunct to midazolam is effective and decreases the time to adequate sedation compared with midazolam alone.
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⨁⨁⨁⨁, **Moderate** ⨁⨁⨁□, **Low** ⨁⨁□□, **or** **Very Low** ⨁□□□
Author: Page et al., 2018 Title: A Prospective Before and After Study of Droperidol for Prehospital Acute	Prospective before and after study	Inclusion: Age 16 or older and attended by ambulance services, had acute behavioral disturbance as the primary reason for ambulance attendance and had a sedation assessment tool (SAT) score of 2 or greater	Primary Endpoint: • Proportion of adverse effects Secondary Endpoint: • Time to sedation • Requirement for additional sedation • Staff and patient injuries • Prehospital time	**GRADE:** B-U **ASSESSMENT:** Possible to uncertain usefulness **QUALITY OF EVIDENCE (GRADE)**: Low ⨁⨁□□ **STRENGTHS:** Droperidol was more effective in comparison to midazolam

<table>
<tr>
<td>Behavioral Disturbance

Comparator: Droperidol 10 mg vs Midazolam dose?</td>
<td></td>
<td>Exclusion: patients<16 years(ethical approval for16 years only), known adverse reactions to midazolam or droperidol, or patients with Parkinson's disease.</td>
<td>Results:
<table>
<tr><th></th><th>Midazolam n=141</th><th>Droperidol n=149</th></tr>
<tr><td colspan="3">Primary outcomes</td></tr>
<tr><td>Adverse events (AE)</td><td>49 AE in 33/141 (23%)</td><td>15 AE in 11/149 (7%)</td></tr>
<tr><td>Airway obstruction</td><td>24 (17%)</td><td>3 (2%)</td></tr>
<tr><td>Desaturation <90%</td><td>6 (4%)</td><td>3 (2%)</td></tr>
<tr><td>Hypoventilation (RR<12)</td><td>3 (2%)</td><td>2 (1%)</td></tr>
<tr><td>Hypotension (SBP <90 mmHg)</td><td>9 (6%)</td><td>3 (2%)</td></tr>
<tr><td>SAT score -3</td><td>7 (5%)</td><td>4 (3%)</td></tr>
<tr><td>Dystonic reaction</td><td>0 (0%)</td><td>1 (0%)</td></tr>
<tr><td>No adverse events</td><td>108 (77%)</td><td>138 (93%)</td></tr>
<tr><td colspan="3">Secondary outcomes</td></tr>
<tr><td>Time to sedation, median</td><td>30 minutes</td><td>22 minutes</td></tr>
<tr><td>Additional sedation, in ambulance</td><td>20/141 (14%)</td><td>6/149 (4%)</td></tr>
<tr><td>Additional sedation, in hospital</td><td>59/141 (42%)</td><td>11/149 (7%)</td></tr>
</table>
Safety:
• There were four (3%) injuries in the midazolam group and six (4%) injuries in the droperidol group to patients and ambulance staff</td>
<td>LIMITATION: recruitment bias although thought to be small

CONCLUSION: IM droperidol is safer and more effective for sedation in patients with acute behavioral disturbance in comparison to midazolam in the prehospital setting.</td>
</tr>
<tr>
<td>Author, title, date
Comparator</td>
<td>Study Design, Number of Patients (n)</td>
<td>Study Population</td>
<td>Endpoint(s)
Result(s)</td>
<td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⨁⨁⨁⨁,
Moderate ⨁⨁⨁□,
Low ⨁⨁□□, or
Very Low ⨁□□□</td>
</tr>
<tr>
<td>Author: Richman et al. 1999

Title: Droperidol for Acute Migraine Headache</td>
<td>Pilot review that collected data via retrospective case series of ED patients with acute migraine (n=37)</td>
<td>Inclusion: Patients with a discharge diagnosis of migraine headache who were treated with IM droperidol 2.5 mg and history of migraine headaches previously diagnosed by a neurologist</td>
<td>Primary Endpoint:
• Relief of symptoms at 30 minutes without further ED intervention required

Secondary Endpoint:
• Incidence of side effects

Results:</td>
<td>GRADE: B-U

QUALITY OF EVIDENCE (GRADE): Low ⨁⨁□□

ASSESSMENT: Uncertain risk

STRENGTHS: Was able to report positive results of IM route of administration of droperidol for</td>
</tr>
</table>

Comparator: Droperidol 2.5 mg IM
 	
Summary: This pilot study determined whether droperidol for migraines was efficacious in the emergency department setting
		or their primary care physician
		
		Exclusion: Patients who presented to the ED with symptoms consistent with migraine headache but without a prior diagnosis, or patients who have a previous history of migraine headache, but received diagnostic studies during their ED stay to rule out other causes of headache
			• Total 37 patients (84% female) had an ED diagnosis of acute migraine where they received IM droperidol 2.5 mg
			• Patients had one or more of the following symptoms: headache (100%), nausea (70%), photophobia (54%), aura (11%), and focal neurological deficits (11%)
			• Of note, analgesics had been used within 24 hours before ED presentation by 62% of patients
			
			Primary Outcomes:
			• At 30 minutes
			  ○ 30 patients (81%) had symptomatic relief
			  ○ 2 (5%) felt partial relief but required rescue medication
			  ○ 5 (14%) had no relief of symptoms
			
			Secondary Outcome:
			• Adverse reactions were uncommon
			  ○ 5 (14%) patients suffered from drowsiness
			  ○ 3 (8%) patients experienced mild akathisia
			• In each case of these cases, the extrapyramidal symptoms were successfully relieved with diphenhydramine
				the treatment of acute migraine. Low incidence of minor side effects.
				
				LIMITATIONS: Retrospective review, small sample size, automatic bias due to unblinded nature and providers at the center where this study was conducted regularly used droperidol. This was a pilot study where it is difficult to assess external validity.
				
				CONCLUSION: Droperidol 2.5 mg IM may be a safe and effective therapy for the ED management of acute migraine headache.

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Weaver et al., 2004 Title: Droperidol vs prochlorperazine	Randomized, blinded, controlled (n=96)	Inclusion: ≥18 years old, presented to ED triage with a headache and had a normal neurological examination	Primary Endpoint: • The number of subjects in each group achieving at least 50% pain relief at 30 min Secondary Endpoint:	**GRADE:** B-U **QUALITY OF EVIDENCE (GRADE): Moderate** ⊕⊕⊕□ **ASSESSMENT:** Uncertain risk

<table>
<tr>
<td>for the treatment of acute headache

Comparator: Droperidol 2.5 mg IV vs prochlorperazine 10 mg IV</td>
<td></td>
<td>Exclusion: T≥38°C (100.4°F), exhibited nuchal rigidity, or had thunderclap onset of the headache, self-treatment with a pain medication or antiemetic in the 4 h before arrival, history of carbon monoxide exposure, peripheral vascular disease, cancer, or HIV infection, pregnancy, allergy to study medications, inability to speak or understand English, and lack of telephone for follow-up contact</td>
<td>

Identifies mean change in pain intensity, the proportion requiring rescue medications from 30 to 60 min, and the incidence of akathisia and other adverse events.

Results:
Primary Outcome:

83.3% in the droperidol group and 72.3% in the prochlorperazine group had 50% pain reduction at 30 min (p<0.01)
The mean decrease in headache intensity at 30 min

Droperidol: 79.1% (SD 28.5%)
Prochlorperazine: 72.1% (SD 28.0%) (p = 0.23; 95% CI −4.6, 18.5)

Secondary Outcome:

No significant difference in the rate of decreased pain intensity between the two study groups over the first 60 min (p = 0.50)
No significant differences at 30 min for percent decrease in nausea (p = 0.22) or level of alertness (p = 0.98)
6 study participants in each group required rescue analgesics (p = 1.0, 95% CI −13.2 to 13.2)
14 (14.6%) study participants experienced akathisia during the first 60 min

Droperidol: 5 (10.5%)
Prochlorperazine: 9 (18.8%) (p = 0.25; 95% CI −22.4, 5.7)

No other adverse events were spontaneously reported in either group

Primary Endpoint:

Categorical Relief at 30 Minutes

<table>
<tr><th>Percent Relief</th><th>Droperidol (n = 48)</th><th>Prochlorperazine (n = 47)</th><th>p value</th><th>One-sided 95% CI for difference</th></tr>
<tr><td>≥ 50%, (%)</td><td>40 (83.3)</td><td>34 (72.3)</td><td>< 0.01</td><td>−2.9, 100</td></tr>
<tr><td>≥ 75%, (%)</td><td>31 (64.6)</td><td>26 (55.3)</td><td>0.03</td><td>−7.2, 100</td></tr>
<tr><td>100%, (%)</td><td>26 (54.2)</td><td>18 (38.3)</td><td>< 0.01</td><td>−0.7, 100</td></tr>
</table>

24-h discharge follow-up: 83 (86.5%) and 40 of them were in the droperidol group and 43 were in the prochlorperazine group
Reported headache

Droperidol: 27.5% (11/40)
Prochlorperazine: 34.8% (15/43) (p = 0.47; 95% CI −27.2 to 12.5)

</td>
<td>STRENGTHS: Strong percentage of follow up post-discharge.

LIMITATIONS: Did not classify the type of headaches or standardized the criteria, sampling was non-consecutive and may not be generalizable to the community setting due to setting was in academic medical centers. This study was not double-blinded that might stimulate bias. The study was terminated early due to shortages of prochlorperazine and the recent black boxed warning on droperidol

CONCLUSION: The study suggests that droperidol and prochlorperazine provide similar pain reduction for headaches in Emergency Department patients with a similar incidence of akathisia.</td>
</tr>
</table>

			• Mean headache intensity at 24-h using a verbal 0-10 pain intensity scale
			  ○ Droperidol: 4.7 (SD 2.1)
			  ○ Prochlorperazine: 5.0 (SD 2.7) (p = 0.78)
			• Supplemental analgesic usage
			  ○ Droperidol: 13 (32.5%)
			  ○ Prochlorperazine: 18 (41.9 (p = 0.38)
			• Akathisia at 24 h after discharge
			  ○ Droperidol: 2.5% (1/40)
			  ○ Prochlorperazine: 14% (6/43) (p = 0.06; CI −22.9%, 0.0%)
			• The 24-h akathisia follow-up was based only on the patient's self-report and not on the investigator's rating, as was done during the first 60 min
			• Twenty-seven (67.5%) of the droperidol group and 28 (65.1%) of the prochlorperazine group reported they had returned to normal daily activities (p = 0.82)	

Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Endpoint(s) Result(s)**	**Grade Bias Assessment Quality of the Evidence (GRADE) High ⊕⊕⊕⊕, Moderate ⊕⊕⊕□, Low ⊕⊕□□, or Very Low ⊕□□□**
Author: Braude et al., 2006 Title: Antiemetics in the ED: a randomized controlled trial comparing 3 common agents Comparator: Droperidol 1.25 mg; metoclopramide 10 mg; prochlorperazine 10 mg; saline placebo injection	Randomized, placebo-controlled, double-blind trial (n=97)	Inclusion: Adult ED patients complaining of nausea	Primary Endpoint: • Compare efficacy of three intravenous antiemetic medications in ED patients complaining of moderate to severe nausea Results: • Twenty-two patients received droperidol, 25 received metoclopramide, 24 received prochlorperazine and 26 received placebo • Droperidol (-54.5 mm) was significantly better than metoclopramide (-40.2 mm) or prochlorperazine (-40.5 mm) at reducing nausea at 30 minutes (P = 0.04) • There were no significant differences in rescue medication or patient satisfaction Safety Endpoint: • Droperidol had significantly higher akathisia at 24 hours follow up (71.4% vs 23.5%)	**GRADE:** U **QUALITY OF EVIDENCE (GRADE):** Very Low ⊕□□□ **ASSESSMENT:** Uncertain risk of bias **STRENGTHS:** Provided comparison of droperidol versus other antiemetic medications used in ED **LIMITATIONS:** VAS scale for nausea was not validated during the study was conducted. Adverse effects like akathisia were self-reported. Study did not include a true placebo group. Medications that might stimulate nausea and vomiting were not excluded.

<table>
<tr><td></td><td></td><td></td><td></td><td>CONCLUSION: IV droperidol was more effective than metoclopramide or prochlorperazine but caused more extrapyramidal symptoms.</td></tr>
<tr><td>Author, title, date
Comparator</td><td>Study Design, Number of Patients (n)</td><td>Study Population</td><td>Endpoint(s)
Result(s)</td><td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td></tr>
<tr><td>Author: Nuttall et al., 2007

Title: Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population?

Comparator:
A retrospective review analyzing patients who had undergone surgery with general anesthesia or central neuraxial blockade and the associated utilization of droperidol 3-years before- and 3-years after the addition of the black box warning.</td><td>Retrospective chart review

N=4528 patient charts reviewed</td><td>Inclusion: all patients that required anesthesia or central neuraxial blockade during the 3-year time period from July 1998 to June 2005

Exclusion: TdP occurred before surgery or droperidol exposure, TdP occurred > 48 hrs postoperatively</td><td>Primary Endpoint:
• The occurrence of TdP within 2 days post-surgery

Other Endpoints:
• The frequency of droperidol use was extrapolated for each time period using data from random sampling
• Droperidol exposure from a random sample of 150 patients was extracted from before and after the BBW

Results: N=4528
<table><tr><th></th><th>QT prolongation, TdP, or death within 48h post-op:</th><th>Droperidol exposure from random 150 sample</th></tr><tr><td>Before BBW</td><td>2,321/139,932 (1.66%)</td><td>16,791/139,932 (12%) - none experienced documented TdP</td></tr><tr><td>After BBW</td><td>2,207/151,256 (1.46%)</td><td>0%</td></tr></table>• During the period before the black box warning 2,321/139,932 patients (1.66%) had QT prolongation, TdP, or death within 48 h after surgery
• No patients were identified who clearly developed TdP before the black box warning
• There was one patient for whom the cause of death could not positively be ruled out as due to TdP
• In the time period after the black box warning 2,207 patients (1.46%) had documented QT prolongation, TdP, or death within 48 h after surgery, including only two cases (<0.1%) of TdP. Neither of those cases received droperidol
• The incidence of droperidol exposure was approximately 16,791 (12%) (95% confidence interval, 10,173-25,607 (7.3-18.3%)) before the black box warning and 0% after placement of the black box warning on droperidol</td><td>GRADE: U

ASSESSMENT: High risk

QUALITY OF EVIDENCE (GRADE): Low ⊕⊕□□

STRENGTHS: The study assessed droperidol exposure before and after the implementation of the BBW. The study found that there was only one death after exposure of droperidol and was not able to pinpoint droperidol was the cause of the death.

LIMITATIONS: The primary endpoint of this study was determining the occurrence of TdP after surgery and not droperidol. The other endpoint mainly addressed droperidol, but it was a small subgroup analysis that was underpowered. The study to rely on notation in patient records to provide a diagnosis after a cardiac event had occurred due to the difficulty of capturing TdP with a 12-lead electrocardiogram due to the brevity of the cardiac rhythm. Additionally, some patients did not obtain an ECG pre-operatively thereby determining change in QTc difficult. Furthermore, the study captured patients who died within 48 hours after therefore non-fatal, transient TdP was not captured. Lastly, the study assessed droperidol exposure based on a sample size of 150 patients and estimated the total exposure rate.</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td>

- Using the conservative estimate of 10,173 exposed patients, the upper bound (based on a 95% CI) for the rate of TdP in patients receiving droperidol is 3.6 per 10,000

Safety:

- One patient of the 456 patients who died within 48 hours after surgery during the time before the black box warning whom the cause of death could not positively be ruled out as due to TdP. 48-year-old, obese (140 kg, 165 cm) women who received 1.25 IV droperidol and 4 mg ondansetron
- Patient was treated with epinephrine, atropine and amiodarone for atrial fibrillation cause of death ruled due to acute hypoperfusion and acute pneumonitis; baseline electrocardiogram was not performed
- In the period after the black box only 2 patients of the 2,207 patients had documented TdP, however, neither patient received droperidol

</td><td>

CONCLUSION: This study found that no change in the incidence of TdP with droperidol versus no droperidol, therefore, the BBW therefore the BBW is excessive and unnecessary.

OTHER INFORMATION: a random sample of 150 surgical patients during each time interval was selected to estimate the droperidol use for each time period. With the sample size of 150 patients, they estimated the percentage of droperidol use before the BBW to approximately ±5% based on the width of the 95% CI

</td></tr>
<tr><td>Author, title, date
Comparator</td><td>Study Design, Number of Patients (n)</td><td>Study Population</td><td>Endpoint(s)
Result(s)</td><td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td></tr>
<tr><td>

Author: Miner et al. 2001

Title: Droperidol vs. prochlorperazine for benign headaches in the emergency department

Comparator: Droperidol, 5 mg IM or 2.5 mg IV, or prochlorperazine, 10 mg either IM or IV

</td><td>

Prospective, single-blind clinical trial of droperidol vs prochlorperazine in the treatment of adult ED patients with the clinical diagnosis of benign headache

December 1,1999 – July 1, 2000 (n=168)

</td><td>

Inclusion: Adults 18-60 yo and had 1) a ‘‘benign headache’’ defined by the examining physician to be without an identifiable etiology from history, physical examination, laboratory analysis, or imaging studies (including, but not limited to, headache due to trauma, subarachnoid hemorrhage, meningitis, intracerebral bleed, cranial tumor, sinusitis, dental pathology, temporomandibular joint dysfunction, glaucoma, or systemic infection) 2) The physician intended to treat

</td><td>

Primary Endpoint:

- Measurement of droperidol side effects and pain perception as measured on a 100-mm visual analog scale (VAS) at baseline, 30, and 60 minutes after medication was given

Results:

- A total of 178 patients consented, but 168 were used in the data analysis.

	IM*	IV*	Total
Droperidol	49 (57.6%)	33 (53.2%)	82 (48.8%)
Prochlorperazine	57 (68.7%)	29 (46.7%)	86 (51.2%)

*The route of delivery of the medication was left to the discretion of the treating physician

Outcomes:

	Droperidol	Prochlorperazine	p-value
30-minute VAS (95% CI)	33.1 mm (26.4, 39.7)	40.6 mm (37.9, 47.3)	0.03

</td><td>

GRADE: U

QUALITY OF EVIDENCE (GRADE): Moderate ⊕⊕⊕□

ASSESSMENT: High risk

STRENGTHS: This study demonstrated a significant difference in the changes from baseline VAS scores between patients with benign headaches treated with droperidol and prochlorperazine. The difference is also seen for clinically significant changes in the VAS (>50%). The absolute and relative reduction in pain severity was greater in the droperidol group at 60 minutes, but not at 30 minutes. These findings indicate that droperidol at the doses used here was superior for treating headache pain in this headache population.

</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>headache pain with one of the two medications

<u>Exclusion</u>: pregnant, breast-feeding, history of hypersensitivity to prochlorperazine or droperidol neuroleptic malignant syndrome, hypotension, cardiac arrhythmia, hepatic or renal dysfunction, or a suspicion of a malignant headache, or refused to provide prospective informed consent</td>
<td>
<table>
<tr><td>Change in VAS from baseline at 30 minutes (95% CI)</td><td>60.7% (53.4, 67.9)</td><td>48.7% (41.3, 56.1)</td><td>0.011</td></tr>
<tr><td>60-minute VAS (95% CI)</td><td>16.3 mm (10.7, 21.8)</td><td>28.9 mm (21.9, 35.9)</td><td>0.007</td></tr>
<tr><td>Change in VAS from baseline at 60 minutes (95% CI)</td><td>81.4% (76.1, 86.8)</td><td>66.9% (59.9, 73.9)</td><td>0.001</td></tr>
<tr><td>Number (%) of patients with >50% change in VAS at 30 minutes</td><td>50 (60.9%)</td><td>38 (44.2%)</td><td>0.09</td></tr>
<tr><td>Number (%) of patients with >50% change in VAS at 60 minutes</td><td>74 (90.2%)</td><td>59 (68.6%)</td><td>0.017</td></tr>
<tr><td>Rescue medications given
Meperidine
Morphine
Hydrocodone
Ketoralac
Ibuprofen</td><td>13 (15.9%)

13 (15.8)
1 (1.2%)
1 (1.2%)
1 (1.2%)
0 (0%)</td><td>18 (20.9%)

10 (11.6%)
0 (0%)
2 (2.3%)
0 (0%)
1 (1.2%)</td><td>0.12</td></tr>
</table>
<u>Side effects:</u>
<table>
<tr><th></th><th>Droperidol</th><th>Prochlorperazine</th><th>p-value</th></tr>
<tr><td>Occurrence of side effects</td><td>13 (15.2%)</td><td>8 (9.6%)</td><td>0.19</td></tr>
<tr><td>Dystonia
Akathisia
Decreased loss of consciousness</td><td>1 (1.2%)
5 (6.1%)
7 (8.5%)</td><td>0 (0%)
7 (8.1%)
1 (1.2%)</td><td></td></tr>
</table>
</td>
<td>LIMITATIONS: No specific criteria for the definition of benign headaches were used except the clinician's judgment. Investigators were not blinded to the study drug. Lack of randomization of the route of administration. The physician determined IV or IM route prior to entering the patient in the study. Medication dosing.

CONCLUSION: Based on the results of this study, we conclude that when a physician intends to treat a benign headache with either prochlorperazine or droperidol, droperidol at the doses studied here has superior efficacy, whether given IM or IV.</td>
</tr>
<tr>
<td>Author, title, date
Comparator</td>
<td>Study Design, Number of Patients (n)</td>
<td>Study Population</td>
<td>Endpoint(s)
Result(s)</td>
<td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td>
</tr>
<tr>
<td><u>Author</u>: Kao et al. 2003</td>
<td>Literature search via MEDLINE,</td>
<td>N/A</td>
<td><u>Results:</u></td>
<td>GRADE: N/A

QUALITY OF EVIDENCE (GRADE): N/A</td>
</tr>
</table>

<table>
<tr>
<td>Title: Droperidol, QT prolongation, and sudden death: What is the evidence?</td>
<td>EMBASE and the International Pharmaceutical Abstracts Database with the subject headings “Droperidol,” “Torsades de pointes,” “Sudden death,” and “Arrhythmia.” “QT prolongation” . (n=11 articles reviewed)</td>
<td></td>
<td>

Three clinical studies, 1 published abstract, and 7 case reports were reviewed. Available post marketing surveillance data (MedWatch reports) were also reviewed.
Applying the criteria of evidence-based medicine and Hill’s criteria, the evidence is not convincing for a causal relationship between therapeutic droperidol administration and life-threatening cardiac events.

Droperidol and QTc prolongation case reports:
<table>
<tr><th>Reference</th><th>TdP (Y/N)</th><th>Potential Alternative Explanations</th></tr>
<tr><td>Guy et al</td><td>Yes</td><td>Rechallenge confirmed that droperidol resulted in QT prolongation; significant arrhythmia occurred the day after droperidol was administered.</td></tr>
<tr><td>Frye et al</td><td>No</td><td>Yes, haloperidol</td></tr>
<tr><td>Frye et al</td><td>No</td><td>Yes, fluphenazine</td></tr>
<tr><td>Faigel et al</td><td>Yes</td><td>Yes, vasopressin infusion, hypokalemia</td></tr>
<tr><td>Thomas and Cooper</td><td>Unknown</td><td>Yes, thioridazine</td></tr>
<tr><td>Michalets et al</td><td>Yes</td><td>Yes, preexisting QTc prolongation, hypokalemia, possible drug interaction between cyclobenzaprine and fluoxetine resulting in the pre- operative QTc prolongation</td></tr>
<tr><td>Shigeyama and Yanagidani</td><td>Chaotic ventricular dysrhythmia</td><td>Yes, preexisting QTc prolongation</td></tr>
</table>
</td>
<td>ASSESSMENT: Uncertain risk

STRENGTHS: Assessed case reports with potential alternative explanation of the prolonged QTc

LIMITATIONS: Was not strong enough to potentiate a meta-analysis from the literature search they performed. The recent black box warning appears to have originated from postmarketing surveillance data rather than data reported in the peer-reviewed medical literature. Ongoing monitoring of drug safety and more definitive study appear appropriate.</td>
</tr>
<tr>
<td>Author, title, date
Comparator</td>
<td>Study Design, Number of Patients (n)</td>
<td>Study Population</td>
<td>Endpoint(s)
Result(s)</td>
<td>Grade
Bias Assessment
Quality of the Evidence (GRADE)
High ⊕⊕⊕⊕,
Moderate ⊕⊕⊕□,
Low ⊕⊕□□, or
Very Low ⊕□□□</td>
</tr>
<tr>
<td>Author: Perkins et al., 2015

Title: American Academy of Emergency Medicine Position Statement:</td>
<td>Literature review: MEDLINE search from January 1995 to January 2014 (n=35 articles)</td>
<td>Inclusion: All studies involving human subjects and written in the English language and containing the keywords: droperidol/Inapsine®

Exclusion: Articles studying multiple medication</td>
<td>Primary Endpoint:

Determine the appropriate use and safety of droperidol ED management of patients
Evidence supporting therapeutic efficacy, role of ECG/monitoring and maximal dosing for droperidol

Results:</td>
<td>GRADE: N/A

QUALITY OF EVIDENCE (GRADE): N/A

ASSESSMENT: Low risk

STRENGTHS: Numerous well-designed studies comparing clinical efficacy and safety of droperidol</td>
</tr>
</table>

Safety of Droperidol Use in the Emergency Department		adverse interactions including droperidol were not included	• A total of 35 articles were deemed appropriate to be pulled for additional screening • These articles include meta-analysis (n = 1), randomized controlled trials (n = 22), retrospective cohort studies (n = 10), and case series/case report (n = 2)	**LIMITATIONS:** The search parameters used for finding relevant articles regarding droperidol along with the quality and quantity of the available literature were potential limitations for this clinical question review. **CONCLUSION:** This review of the literature supports the use of droperidol with a high level of evidence. Droperidol is an effective and safe medication in the treatment of nausea, headache, and agitation. The literature search did not support mandating an ECG or telemetry monitoring for doses <2.5 mg given either IM or IV Intramuscular doses of up to 10 mg of droperidol seem to be as safe and as effective as other medications used for sedation of agitated patients.
Author, title, date Comparator	**Study Design, Number of Patients (n)**	**Study Population**	**Result(s)**	**Grade** **Bias Assessment** **Quality of the Evidence (GRADE)** **High** ⊕⊕⊕⊕, **Moderate** ⊕⊕⊕□, **Low** ⊕⊕□□, **or** **Very Low** ⊕□□□
Author: Gottlieb et al., 2018 Title: What Is the Efficacy of Droperidol for the Management of Acute Psychosis-Induced Agitation?	Systematic review (n=733)	Inclusion: This systematic review included all randomized controlled trials that compared droperidol with any other treatment for acute psychotic illnesses (eg, schizophrenia, schizoaffective disorder, mixed affective disorders, acute mania, brief psychotic episodes). Studies in which the majority of participants were thought to have a form of mental illness were included. Electronic searches were performed with the Cochrane	Results: • The search strategy identified 14 total studies, of which 6 (n=733 total patients) met the inclusion criteria • Droperidol was associated with an increased likelihood of tranquilization • Compared to placebo, droperidol had a significant difference in tranquilization at 30 minutes • Other agents like haloperidol, olanzapine, and midazolam showed no significant differences (Table x) • Compared with haloperidol, droperidol was associated with a decreased risk of needing additional medication after 60 minutes (2 randomized controlled trials; n=255; risk ratio=0.37; 95% confidence interval 0.16 to 0.90) • There was no difference in the need for additional medication at 60 minutes when droperidol was compared with midazolam or olanzapine Table 24. Comparison of droperidol with alternate pharmaceutical agents with respect to tranquilization.	GRADE: N/A **ASSESSMENT:** N/A **QUALITY OF EVIDENCE (GRADE)**: Low risk **STRENGTHS:** This systematic review included all randomized controlled trials that compared droperidol with any other treatment for acute psychotic illnesses (eg, schizophrenia, schizoaffective disorder, mixed affective disorders, acute mania, brief psychotic episodes). The review encountered low rates of QT prolongation and no cases of torsades de pointe. **LIMITATIONS:** Only half of the studies were conducted in an ED. No studies assessed patients managed in the out-of-hospital

		Schizophrenia Group Register of Trials through December 18, 2015. Exclusion: Quasi-randomized studies (eg, studies performing drug allocation by day of week) and studies in which greater than 50% of participants were lost to follow-up, in which participants had nonpsychiatric diagnoses (eg, alcohol intoxication), or in which treatment for the illness was not specified were excluded.	<table><tr><th>Difference in Tranquilization at 30 Minutes</th><th>No. of Participants (No. of Studies)</th><th>RR (95% CI)</th></tr><tr><td>Droperidol vs placebo</td><td>227 (1)</td><td>1.18 (1.05–1.31)</td></tr><tr><td>Droperidol vs haloperidol</td><td>228 (1)</td><td>1.01 (0.93–1.09)</td></tr><tr><td>Droperidol vs olanzapine</td><td>221 (1)</td><td>1.02 (0.94–1.11)</td></tr><tr><td>Droperidol vs midazolam</td><td>153 (1)</td><td>0.96 (0.72–1.28)</td></tr></table> Safety • Adverse events rates were very low with droperidol, with no significant difference in the risk of cardiac dysrhythmias or airway complications noted in any of the trials.	environment, which is a common route for these patients to arrive at the hospital. The data were available on 733 patients, most outcome assessments consisted of approximately 200 patients. This review did not include a recent randomized controlled trial demonstrating similar efficacy between olanzapine and droperidol with improved sedation noted in a third group who received droperidol with midazolam. **CONCLUSION:** Droperidol is effective for the treatment of acute psychosis-induced aggression or agitation, with a low risk of adverse events compared with placebo, olanzapine, haloperidol, and midazolam.