

## Journal Club Synopsis

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### **What does the literature say about the safety and efficacy of droperidol?**

**Clinical Scenario:** Case: You are working a very busy "E" shift over a weekend and it appears the 0200 bus has arrived with a bolus of patients. You've got a 75 year old lady in bed 5 with undifferentiated abdominal pain that looks sick, a 52 year old man in with RVR with dyspnea and chest pain in 6 and a potpourri of other patients scattered throughout the department. A squad rolls in with police close in tow, with taser wires sticking out of her chest, yelling various colorful epithets about police and EMS while struggling (restrained) in the gurney. You find she is a 45 year old female, found outside a local bar extremely altered, agitated and uncooperative. She has admitted drinking alcohol to EMS but that is all you know about her. She was shot with 2 sets of taser darts (only because a third set missed) and has been marginally controlled with electricity.

On greeting her, she tell you "@&\$! Off you &\$@!" she then proceeds to kick a nurse, punch a PCT, and spit into the face of a security guard and another nurse. Her HR is 145, BP is 200/97, and she appearing to be exchanging gases well while cursing you out. You have little time to control the situation and protect your staff and this patient from herself while performing any diagnostic testing to rule out life threatening diseases. This is a job for an effective chemical takedown. You think "What are my options for chemical restraints?" Many of your attendings use the old "B-52". You have used the B52, Geodon and Versed in the past for chemical restraint. You disregard ketamine with this patient because her vitals and overall presentation are also consistent with a sympathomimetic toxidrome and she may be psychotic also. Hey! Scott Weingart has talked about Droperidol on a podcast, so it must be good... Right? But what about that QT prolongation and the black box warning? Hmmm.

#### **Introduction:**

Many times in medicine, we are taught anecdotally how to handle problems – so I wanted to know how effective droperidol actually is the chemical takedown of agitated patients. I also hoped finding articles on this subject would shed some light on the “Black-Box” warning that droperidol carries for QT prolongation. I chose these articles for a few reasons. I wanted to find decent articles and got lucky with 3 RCT’s. I wanted to host a journal club that 1.) Controversial 2.) Might actually influence your practice and 3.) Would generate good discussion. I think we succeeded on at least numbers 1 and 3.

#### **Article 1:**

Thomas H Jr, Schwartz E, Petrilli R. Droperidol versus haloperidol for chemical restraint of agitated and combative patients. Ann Emerg Med. 1992 Apr;21(4):407-13.

This article predated the FDA black box warning on droperidol and sought to simply look at which drug was better, haloperidol or droperidol. This was an RCT (blinded, but not placebo controlled) out of Wake Forest with an n=68 with fairly good distribution between droperidol and haloperidol, IV and IM. The article found that in agitated patients in the ED, not quickly attributable to an organic cause, 5mg IM droperidol worked faster to reduce agitation than 5mg IM haloperidol. There was not a statistical difference in IV formulations. Side effects were mild and comparable in either group. No mortality was observed. Some issue with the study included a non-standard agitation scale, heterogeneity of samples, and exclusion of some patients for re-dosing at 30 minutes.

**Article 2:** Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. Ann Emerg Med. 2010 Oct;56(4):392-401.e1. doi: 10.1016/j.annemergmed.2010.05.037.

The DORM study, in our opinion, was a well-thought out and informative study, which also sought to seek QTc problems. This study was a BRCT out of Australia that centered on the overall ED algorithm of dealing with agitated patients. It was agreed that necessary steps were undertaken before using chemical restraint, in contrast to the first study where the inclusion criteria were 2 physicians agreeing that the patient was agitated due to a non-reversible cause. The DORM study used verbal de-escalation and show of force prior to using medications. Patients were randomized to receive either 10 mg droperidol, 10 mg of midazolam or 5 mg midazolam + 5 mg droperidol. I would have like to see more patients in this study, 91 patients were randomized into arms of 33, 29 and 29, respectively. Droperidol and droperidol with midazolam had the most predictable sedation, typically did not require more medications and had the fastest onset time. Midazolam and droperidol + midazolam were more unpredictable in depth and time of sedation. Midazolam alone was associated with 28% side effects versus 6 and 7% for droperidol and the combination respectively. There were abnormal QT intervals seen, 2 in each of the droperidol and midazolam groups and 4 in the combination group – 31/33 in the droperidol alone group had an EKG for evaluation. The authors concluded, “there was no evidence of QT prolongation associated with droperidol.” However they clearly list 2 cases of an abnormal QT and do not specify. It would have been useful to quantitate all QT changes in all arms. If this study had been adequately powered to detect a difference in QT prolongation, I would agree with them, but they did not. Also, we have no idea of what clinically relevant QT prolongation is.

### Article 3:

Chan EW, Taylor DM, Knott JC, Phillips GA, Castle DJ, Kong DC. 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 Jan;61(1):72-81. doi: 10.1016/j.annemergmed.2012.07.118. Epub 2012 Sep 13.

The third article was a multi-center RDBPCT comparing effectiveness of olanzapine or droperidol PLUS midazolam for the acutely agitated patient. This was an important study because we rarely employ a single agent in chemical restraint – e.g. the B-52; however, there are no good clinical data to support the efficacy of combination regimens. This was a much larger study than the previous one with n=336. The basic design: in three arms, acutely agitated patients would receive either saline, droperidol or olanzapine IV then shortly thereafter receive increasing doses of midazolam 2.5-5 mg until sedation was achieved. As expected, participants receiving two drugs were 1.6 times to be sedated at any given time. Median time to sedation was 6 minutes with droperidol, 5 minutes with olanzapine and 10 minutes with placebo (+Versed.) This ties back into the original clinical scenario – how important at 5-6 minutes with an agitated patient in a busy ER?

The study showed similar efficacy with olanzapine and droperidol – both are safe and effective and faster than when compared with IV midazolam alone. It is important to note that benzodiazepine +/- antipsychotics had similar adverse events. Some limitations brought up: these meds studied were IV, not IM, and IV's can be difficult to obtain in the acutely agitated patient. One of our faculty members brought up an excellent point concerning the “black box” surrounding droperidol – namely that of prolonged QTc prolongation. His comment was that the acute elevation in QTc is a rapid and transient phenomenon and EKG's were obtained at 60 minutes if at all and there was no QTc prolongation seen. Baseline EKGs were not obtained because of agitation. QTc study was not a study objective of this trial.

We made the distinction between QTc prolongation and Torsades de Pointes – an elevated QT DOES increase risk for Torsades; however, it certainly does not necessarily preclude it or cause it. Not every person with a prolonged QTc will go into Torsades and die. It was suggested that it may be a better bet to use olanzapine since it is not “black-boxed.”

**Overall Discussion:** I think it's worth inserting the black box warning on droperidol – see below. What is inherently obvious is that this statement has limited your choice of medications. We agree that ALL medications have side effects, but we agreed that this statement is lawyer bait. We individualize the needs of a situation with the needs of the patient and the needs of our department and staff safety. Unfortunately, the FDA's actions are coercive, not only in this particular case, but in all black box warnings because the threat of negligence in a bad outcome is very real. It really *should* be up to us to ascertain risks and benefits of a treatment plan and then enact the plan. Many people said they would consider using droperidol now knowing that it is fast and effective. There are many published reports of its safety, though anecdotal and not RCT quality. The discussion turned to adequate documentation and ensuring that if droperidol is used, the use, risks and benefits are clearly stated in the MDM section. Others maintained that ziprasidone and the B52 are well suited to chemical restraint and are without the contentious black box warning. Many people agreed that they would consider using droperidol in the correct clinical circumstances.

| WARNING  |
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| <b>Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving Inapsine (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.</b>   |
| Due to its potential for serious proarrhythmic effects and death, INAPSINE (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 (see <a href="#">WARNINGS</a> , <a href="#">ADVERSE REACTIONS</a> , <a href="#">CONTRAINDICATIONS</a> , and <a href="#">PRECAUTIONS</a> ).  |
| Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with INAPSINE (droperidol). Based on these reports, all patients should undergo a 12-lead ECG prior to administration of INAPSINE (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, INAPSINE (droperidol) should NOT be administered. For patients in whom the potential benefit of INAPSINE (droperidol) treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2 to 3 hours after completing treatment to monitor for arrhythmias. |
| INAPSINE (droperidol) is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome.   |
| INAPSINE (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.   |

**Bottom line:** Droperidol, by published safety and effectiveness measures is a good drug, and one many still reach for in the acutely agitated patient. The defensive stand is this: if you can get an EKG prior to giving it, droperidol may be an option, but the black box warning clearly states “should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments.” Like Haldol – which also can prolong the QT and thus would preclude the use of droperidol. The pragmatic view is this: If the clinical situation demands it, use it and document it and if you need to defend yourself, there is enough data to support it's safe use.

PS if you haven't read Droperidol—Behind the Black Box Warning by Horowitz et al – it's worth 10 minutes of your time. Horowitz BZ, Bizovi K, Moreno R. Droperidol--behind the black box warning. Acad Emerg Med. 2002 Jun;9(6):615-8.