PGY-3

**Critical Review Form**

 **Cohort Study**

[Calver L, Page CB, Downes MA, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK. The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department. Ann Emerg Med. 2015 Sep;66(3):230-238.e1.](http://pmid.us/25890395)

**Objectives: "to investigate the frequency of  QT prolongation and torsades de pointes in patients administered high-dose (10 mg or more) droperidol in the ED for acute behavioral disturbance. In addition, it aimed to investigate the frequency of other adverse events and the effectiveness of droperidol for sedation." (p. 231)**

**Methods: This prospective, multicenter, observational study was conducted at the EDs of 6 hospitals in Australia between August 2009 and March 2013. Adult ED patients (age 18 years or older) with acute behavioral disturbance, felt to be at risk of harm to self or others, with a score of 2 or 3 on the** [**Sedation Assessment Tool (SAT)**](pmid.us/22151672) **were eligible for inclusion. Patients willing to take oral medication for sedation were excluded. By protocol, patients requiring parenteral medication for sedation in the ED were given high-dose droperidol (10 mg IM or IV as an initial dose) and were monitored using the SAT score. An additional dose was recommended if the patient did not settle within 15 minutes. After the second dose of droperidol, additional medications were administered at the discretion of the treating physician.**

**All patients were monitored via cardiac monitor, pulse oximetry, and noninvasive blood pressure machine, and SAT scores and vital signs were recorded every 5 minutes for 20 minutes, then every half hour thereafter. ECGs were not routinely performed, but were included in the analysis if performed within 2 hours of droperidol administration. The primary outcome was an abnormal QT interval, defined as the QT-HR pair above the "at-risk" line on the QT nomogram within 2 hours of the last droperidol administration. Secondary outcomes were development of torsades de pointes, other adverse events, time to sedation (time until SAT score decreased by 2 points or more or was zero), failed sedation (within 120 minutes), need for additional sedation, oversedation (SAT score -3), and staff injuries.**

**There were 1781 presentations for acute behavioral disturbance during the study period; 1403 of these cases had complete data recorded and were included in the final cohort. The medial age in this cohort was 34 years and 60% were male. At least one ECG was performed within the first 120 minutes in 1091 cases; after excluding 82 patients with repeat admissions, there were 1009 cases included in the ECG safety analysis. The median initial dose and median total dose of droperidol were both 10 mg.**

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| **Critical Review Form: Cohort Study** |
| Guide | Comments |
| **Are the results valid?** |
| **Did experimental and control groups being the study with a similar prognosis?** |
| Did the study address a clearly focused issue?  | Yes. The authors primarily sought to evaluate the safety of droperidol for the management of acute behavioral disturbance in the ED. More specifically, they wanted to evaluate the actual (rather than perceived) risk of QT prolongation following droperidol administration, given the black box warning issued by the FDA for this potential adverse effect. |
| Did the authors use an appropriate method to answer their question? - Is a cohort study a good way of answering the question under the circumstances?  | No. While a prospective cohort study is a reasonable way to answer the posed questions, a large number of potentially eligible patients in this study (~15%) were excluded due to lack of complete records. For the specific question regarding prolongation of the QT interval, over 40% of patients were excluded from analysis because an ECG was not performed within 2 hours of droperidol administration. These high exclusion rates raise the risk of [selection bias](https://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_Bias/EP713_Bias3.html) significantly. |
| Was the cohort recruited in an acceptable way? - Was the cohort representative of a defined population? - Was there something special about the cohort? - Was everybody included who should have been included?  | Uncertain. The authors do not say how exactly patients were recruited, other than to say that inclusion "was determined by ED staff." It is unclear if consecutive patients were included or if this was a convenience sample or if any training was undertaken to ensure staff were aware of the study and informed of inclusion criteria. The authors did not look at patients who were eligible but not included, other than the large number of patients who were recruited but then excluded due to lack of a complete data record. |
| Was the exposure accurately measured to minimize bias? - Did they use subjective or objective measurements? - Do the measures truly reflect what you want them to (have they been validated)? - Were all the subjects classified into exposure groups using the same procedure?  | Yes. The exposure was fortunately very objective (droperidol administration) and easily measured from the medical record. Exposure was determined via the same method for all patients who were included, but the authors did not evaluate for potential differences in dosing, and did not seek to analyze for a potential dose effect. |
| Was the outcome accurately measured to minimize bias? - Did they use subjective or objective measurements? - Do the measures truly reflect what you want them to (have they been validated)? - Has a reliable system been established for detecting all the cases (for measuring disease occurrence)? - Were the measurement methods similar in the different groups? - Were the subjects and/or the outcome assessor blinded to exposure(does this matter)?  | Yes. The authors provide a very in-depth discussion on how the primary outcome (QT prolongation) was measured based on ECG findings. Unfortunately, over a quarter of included patients did not have an ECG performed and hence could not be evaluated for the primary outcome. QT prolongation, while a concerning potential adverse effect of droperidol, is not necessarily a [patient-centered outcome](http://omerad.msu.edu/ebm/Intro/Intro6.html) if it does not lead to a dysrhythmia (i.e. torsades de pointes). |
| Have the authors identified all important confounding factors and have they taken account of the confounding factors in the design (i.e. modelling, regression, propensity analysis, or sensitivity analysis to correct, control or adjust for confounding factors)? | No. The authors did not look at baseline QT duration and the pre-existing presence of QT prolongation for all patients; they also did not perform an in-depth analysis of the use of other QT-prolonging agents during the ED stay, the use of potential QT-prolonging agents at home, or the presence of electrolyte disturbances. |
| Was the follow up of subjects complete and was the follow up of subjects long enough?  | No. A large number of patients was excluded due to lack of complete records and an additional 400 did not have an ECG during the study period. |
| **What are the results?** |
| What are the results of this study?  | * Among 1009 ECGs available, the median QT was 360 ms. Thirteen of these had an abnormal QT duration (1.3%, 95% CI 0.7% to 2.3%).
	+ Two of these patients had a preexisting prolonged QT on ECG performed prior to droperidol administration.
	+ Two patients were receiving methadone, 2 were receiving escitalopram, and 1 was receiving amiodarone.
	+ Excluding patients with another reason for prolonged QT, there were 6 cases of QT prolongation (0.6%, 95% CI 0.2% to 1.4%).
* There were no cases of torsades de pointes.
* The median time to sedation (among 1403 patients) was 20 minutes (IQR 10 to 30 minutes).
* Adequate sedation within 120 minutes was achieved in 97% of patients.
* Adequate sedation was achieved with the initial dose of droperidol in 69.0% of patients (95% CI 66.5% to 71.4%).
* Oversedation occurred in 7.8% of patients.
* There were 71 adverse events in 70 patients (5.0%, 95% CI 3.9% to 6.3%). Hypotension (n = 28) and desaturation (n = 22) were the most common adverse events. One patient who had taken an tricyclic acid overdose required intubation.
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| How precise are the results? (i.e. what 95% CIs were associated with the results?) | See above. |
| Do you believe the results?  | Yes Overall, the incidence of prolonged QT interval was low and no patient suffered torsades de pointes, which I would expect based on prior experience. Both of these outcomes are highly objective and would be difficult to suppress if they occurred. The remainder of results are in keeping with prior experience. |
| **Will the Results Help Me Locally?** |
| Were the study patients similar to my patient? | Somewhat. This study was conducted in several EDs in Australia, and there may be significant differences between the etiologies of agitation in this study and in our population. About half of patients in the study were agitated because of alcohol intoxication; I suspect a much smaller proportion of patients requiring sedation in our ED are intoxicated with alcohol while a higher proportion are intoxicated with other substances or suffering primary psychiatric disorders (psychosis, mania). These differences may not change how droperidol affects the QT interval, however, and the documented safety in this study likely does apply to our patient population. |
| Do the results of this study fit with other available evidence?  | Yes. Despite the previous publication of a [black box warning by the FDA](http://pmid.us/12045077) for droperidol due to anecdotal reports of QT prolongation and torsades the pointes, existing evidence suggests that droperidol's effect on the QT interval is minimal ([Chase 2002](http://pmid.us/12460844), [Isbister 2010](http://pmid.us/20868907)). The current study provides further evidence of the safety of droperidol. |

**Limitations:**

1. **The sedation assessment tool used does not appear to be well-validated.**
2. **All patients who received droperidol were monitored by cardiac monitor, pulse oximeter, and noninvasive BP machine. This is not routine care in our institution and may not be feasible in all patients requiring sedation.**
3. **Nearly 400 eligible patients were excluded entirely due to lack of complete data. Over 40% of eligible patients were excluded from the primary outcome due to lack of an ECG (**[**selection bias**](https://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_bias/ep713_bias3.html)**).**
4. **The authors did not perform any analysis of patients who were eligible for the study but were not included.**
5. **Patients with a SAT score of 1 were included despite the inclusion criteria of SAT score 2 or 3.**

**Bottom Line:**

**This prospective cohort study suggests that droperidol, when given for acute behavioral disturbance in the ED, is safe and does not result in a significant incidence of QT prolongation, torsades de pointes, or other serious adverse events.**