Exploration of the Safety of Droperdiol Use in the ED

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Client: Tran Trinh, UW Pharmacy Resident

Abstract

There are concerns regarding increased risk of arrhythmia when the drug droperidol is used to manage agitation in emergent situations. Data collected on patients in the ED at UW Medicine from 2022-2023 are used to explore what factors increase risk of arrhythmia among patients that were administered droperidol. Analysis shows that agitated patients administered droperidol are more likely to have an arrhythmia than non-agitated patients. Additionally, patients with headaches that are administered droperidol are less likely to have an arrhythmia than patients without headaches.

1 Motivation

Droperidol is a drug that can be used to manage agitation in patients. The current FDA guidelines do not allow droperidol to be used in emergency situations because previous studies have linked this drug to deadly arrhythmias. This is the guideline that UW Medicine follows. However, some other hospitals allow overrides of this guideline. Tran hypothesizes that droperidol is safe to use in the doses administered to treat agitation in the emergency department. She has access to retrospective data of patients who received droperidol which she plans to use to identify the factors that are associated with an increased risk of arrhythmia and quantify such risk. She plans to present her findings to UW Medicine and reopen the discussion of whether or not UW Medicine should allow overrides to the current guidelines that limit droperidol use in emerging situations. This report aims to address the following questions to help Tran with her analysis.

1. Among patients administered droperidol, what factors are associated with an increased risk of arrhythmia?
2. From these identified factors, how can we quantify the increased risk of arrhythmia among patients administered droperidol?
3. Is droperidol administration associated with an increased risk of arrhythmia among agitated patients?
4. Is droperidol administration to agitated patients associated with increased/decreased QTc?
5. How does a practitioner decide whether or not to administer droperidol to a patient based on their risk of an arrhythmia?

2 Data

The data collected contains 650 observations, each of which is a patient in the emergency department who was administered the drug droperidol. The data was collected between 2022 and 2023. The reasons for administration may include any combination of abdominal pain, nausea, agitation, vomiting, or

headache, although it may be unknown for some patients. The frequency of patients exhibiting each of these symptoms is depicted in Figure 1, which shows that the most common use of droperidol was for soothing agitation.

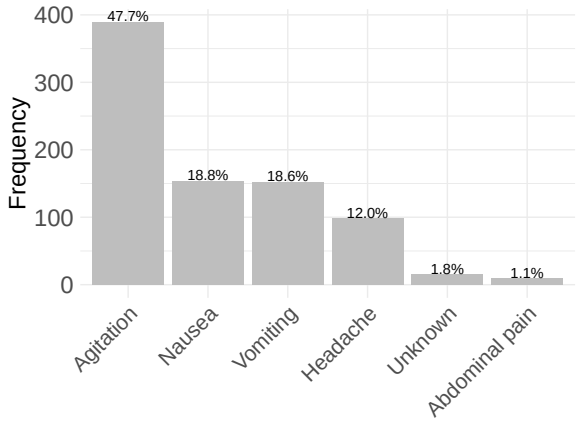


Figure 1: Number and percentage of patients exhibiting each of the reasons for being administered droperidol.

Some data preprocessing was needed in order to isolate the symptoms each patient was experiencing, as well as to make terminology consistent for what was missing data. For example, N/A and - - were converted to NA. There was also a patient with an invalid recorded age of 143 that was converted to NA. There was not a single death recorded in the dataset. For safety precautions, every patient in the dataset was required to stay in the ED for at least 2 hours after drug administration. If the effects of the first dose of the drug were not sufficient within 30 minutes, the patient would receive additional doses. The total amount of droperidol administered to each patient varied from 1.25 mg to 15 mg. Some patients received EKGs with QTc measurements before and/or after the administration of droperidol. Only 15 patients received an EKG before *and* after.

This dataset contains a record of whether a patient had an arrhythmia. Only 45 out of 650 patients, experienced an arrhythmia. The absolute risk of arrhythmia, AR, following droperidol administration is

$$AR = \frac{\#\text{ of patients with an arrhythmia after receiving droperidol}}{\#\text{ of patients that received droperidol}}$$

The point estimate of the absolute risk of arrhythmia (expressed as a percentage) following a dose of droperidol is 6.9%, with a 95% confidence interval of $(5\%, 8.9\%)$.

The only covariates recorded before or at the time droperidol were administered was patient's legal sex, age, reason for droperidol administration, whether an EKG was obtained before droperidol administration, the corresponding measured QTc from the EKG, and the administered dose amount (mg). These are the only variables in the dataset that can be used to predict the occurrence of an arrhythmia following droperidol administration. The total amount administered may include additional doses of droperidol after the first, but for the purposes of this analysis, we will treat this as a predictor of arrhythmia as well.

3 Exploratory Data Analysis

Refer to Figure 2 to visualize the relationship between arrhythmia occurrence and patient's legal sex, age, total administered amount of droperidol, and their QTc measurement before droperidol administration. Refer to Figure 3 to visualize the frequency with the corresponding percentages of various reasons for droperidol administration for patients who did and did not have an arrhythmia.

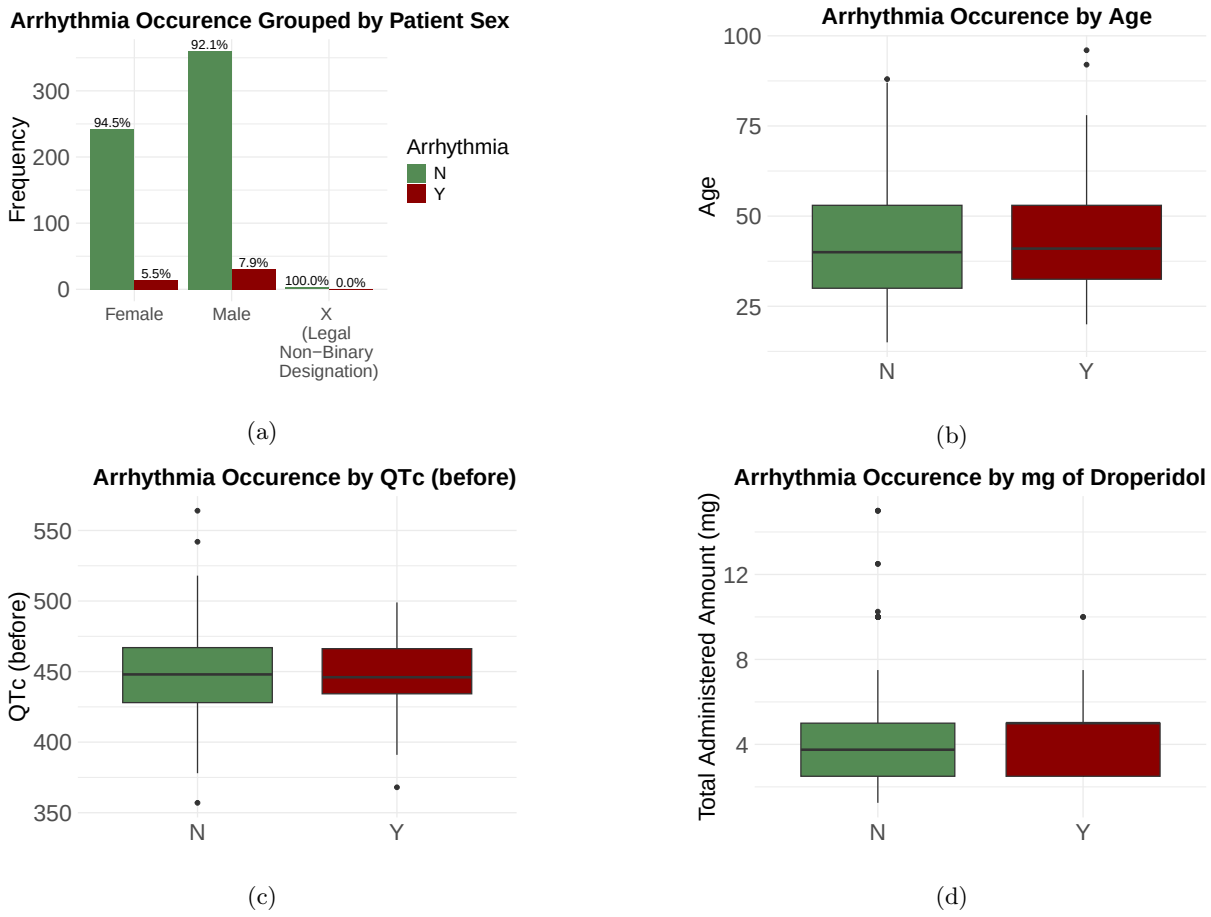


Figure 2: Distribution of counts or box plots of values for various predictor variables recorded in the dataset for patients who did and did not experience an arrhythmia.

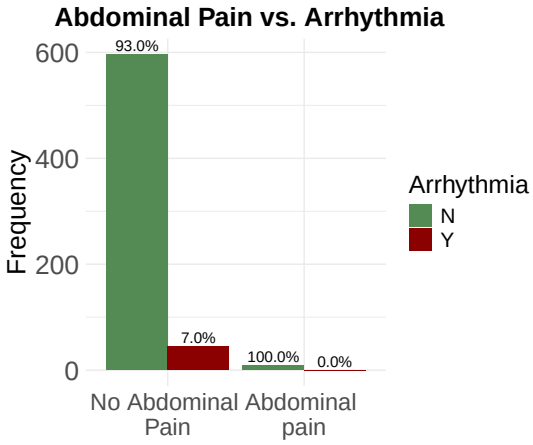
Before fitting a model to quantitatively explore these relationships, it is valuable to explore the correlation between variables. Including correlated variables in a model can cause issues with model fit and interpretation, so if the goal is to do inference on the coefficients, only one of the pair of correlated variables should be chosen to be included in the model. Nausea and vomiting are likely highly correlated because nausea and vomiting tend to occur together, and this is confirmed by Table 1, which shows a 1:1 correlation between nausea and vomiting. Since vomiting is an easier to identify for a patient than nausea, vomiting was chosen as the variable. Tran can choose to include nausea instead of vomiting if that is her preference.

4 Logistic Regression Model

To address the first question, **"Among patients administered droperidol, what factors are associated with an increased risk of arrhythmia?"**, consider the logistic regression model given by the equation:

$$log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_n x_n$$

In this model, p represents the probability that a patient has an arrhythmia, β_0 is the intercept, β_i are the coefficients for the predictor variables, and x_i denotes the values of the observed data for the corresponding predictor variable i for each patient. Note that when answering this question, we are *not* isolating the effect of droperidol on arrhythmia occurrence, but simply identifying what factors are



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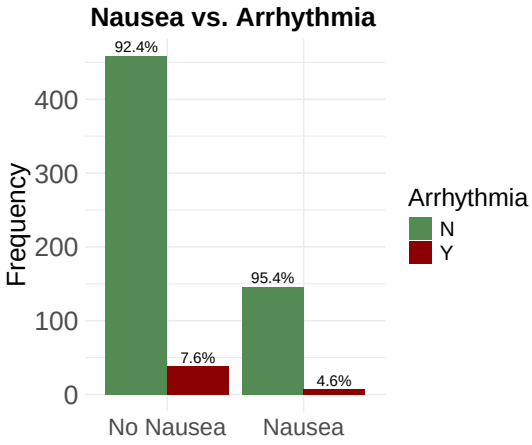

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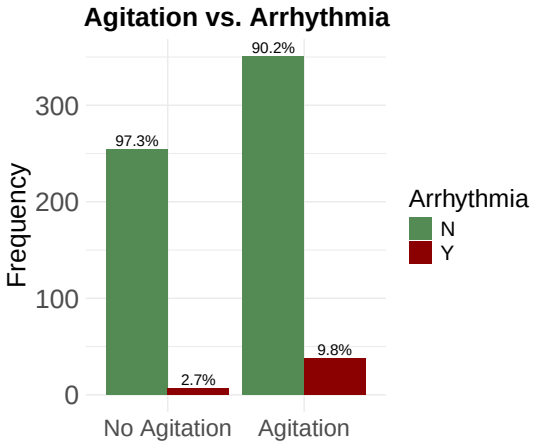

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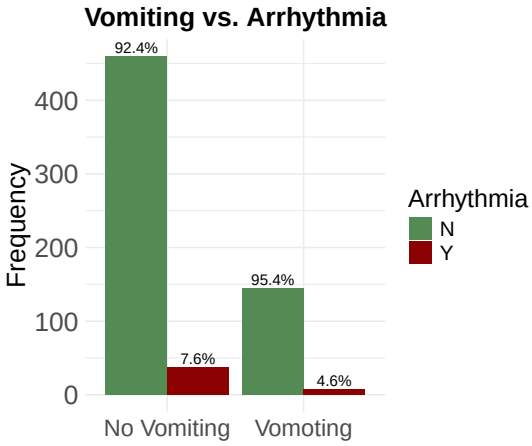

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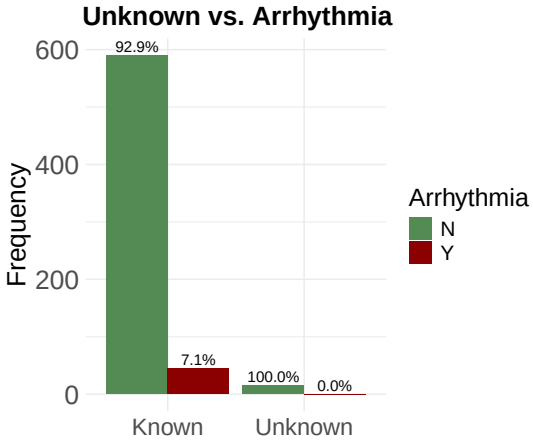

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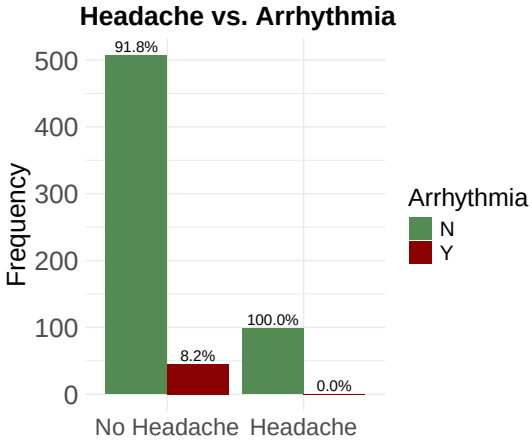

(f)

Figure 3: Distribution of counts for various reasons of droperidol administration recorded in the dataset for patients who did and did not experience an arrhythmia.

	Legal Sex	Age	Total Dose	QTc (before)	Abdominal pain	Nausea	Agitation	Vomiting	Unknown	Headache
Legal Sex	1.00	0.07	0.09	0.14	0.01	-0.07	0.20	-0.08	-0.06	-0.19
Age	0.07	1.00	-0.01	0.12	0.00	-0.09	0.10	-0.09	0.00	-0.03
Total Dose	0.09	-0.01	1.00	0.16	-0.06	-0.29	0.51	-0.28	-0.12	-0.33
QTc (before)	0.14	0.12	-0.16	1.00	-0.10	0.03	0.03	0.03	0.09	-0.10
Abdominal pain	0.01	0.00	-0.06	-0.10	1.00	-0.04	-0.14	-0.07	-0.02	-0.05
Nausea	-0.07	-0.09	-0.29	0.03	-0.04	1.00	-0.64	1.00	-0.09	-0.15
Agitation	0.20	0.10	0.51	0.03	-0.14	-0.64	1.00	-0.64	-0.19	-0.51
Vomiting	-0.08	-0.09	-0.28	0.03	-0.07	1.00	-0.64	1.00	-0.09	-0.15
Unknown	-0.06	0.00	-0.12	0.09	-0.02	-0.09	-0.19	-0.09	1.00	-0.07
Headache	-0.19	-0.03	-0.33	-0.10	-0.05	-0.15	-0.51	-0.15	-0.07	1.00

Table 1: Correlation matrix for some of the predictor variables in the dataset.

associated with an increased risk of arrhythmia among patients that receive droperidol.

Consider the following predictor variables of arrhythmia: patient legal sex, age, reason for droperidol administration, total amount administered (mg) and QTc (before) measurements. Since 75.7% of the QTc (before) measurements are missing, we will exclude this as a predictor variable in the logistic regression model because the model is only fit using the observations with complete data. Additionally, 3 of 650 patients had their age missing, so those observations were removed as well.

A logistic regression model with all the predictor variables, except QTc (before), issues a warning that it is predicting probabilities close to 0 or 1 for some of the observations which can effect model estimates. This could be happening due to *perfect separation*, a phenomenon in which one or more variables perfectly predicts the outcome. Of the patients whose reason for droperidol administration was unknown or a headache, zero of them had an arrhythmia, and hence could explain the possible perfect separation phenomenon occurring. Removing the *Unknown* and *Headache* variables from the logistic regression fixes this issue. The summary of the model can be found in Table 2. In the table, *Total Dose* refers to the total administered amount of droperidol in mg.

	$\hat{\beta}$	Std. Error	p-value
Intercept	-4.733	0.885	8.838×10^{-8}
Sex (Male)	0.104	0.344	0.762
Sex (X)	-13.424	1333.927	0.992
Age	0.007	.010	0.508
Total Dose	0.002	.082	0.982
Abdominal Pain	-12.195	799.084	0.989
Agitation	2.055	0.723	0.004
Vomiting	1.203	0.721	0.095

Table 2: Summary of logistic regression with patient sex, age, total droperidol dose, and reason for droperidol administration as covariates.

Take note of the large standard error for a couple of the estimates in Table 2. This means that the model has high uncertainty regarding the estimate of β for those corresponding variables. Recall that from Figure 2(a), we know that very few patients had the legal non-binary designation X, none of which had an arrhythmia. Additionally, from Figure 3, we know that none of the patients with abdominal pain had an arrhythmia. Since these counts are very small (< 10), zero in fact, statistical inference on these variables, including the standard errors and p-values, is not reliable.

From Table 2, we also see that the only variable with a p-value less than 0.05 is the Agitation variable, and the value of the coefficient is 2.055 with a 95% confidence interval of (0.748, 3.581). This means that we can say with 95% confidence that when a patient is agitated and administered droperidol, while holding

Variable	Odds Ratio 95% CI	p-value
Unknown	(0, 3.8)	0.6154
Headache	(0, 0.5)	0.0008163
Abdominal pain	(0, 6.9)	1
Sex (X)	(0, 33.0)	1

Table 3: Results of Fisher's Exact Test to test the null hypothesis that each variable is independent of arrhythmia occurrence.

all other covariates constant, the odds of the patient having an arrhythmia is almost 8 ($e^{2.055} \approx 7.81$) times higher than for a non-agitated patient.

Having identified that agitation is associated with an increased risk of arrhythmia among patients administered droperidol, we may now be interested in addressing the question, **"How can we quantify the increased risk of arrhythmia among patients administered droperidol?"** We already mentioned above that the odds of an agitated patient having an arrhythmia is almost 8 times higher than a non-agitated patient, but we can go one step further and estimate the absolute risk of arrhythmia among agitated and non-agitated patients. The point estimate of the absolute risk of arrhythmia among agitated patients that received droperidol is 9.9%, while the point estimate of the absolute risk of arrhythmia among non-agitated patients that received droperidol is 2.6%. A Fisher's Exact Test concludes that the difference between these two absolute risk estimates is significant ($p - value = 0.0002$), validating our findings from the logistic regression. In terms of practical significance, we leave it to Tran and UW medicine to decide whether this difference in absolute risk of arrhythmia among agitated and non agitated patients warrants taking appropriate precautions regarding administering droperidol to agitated patients. That being said, it is unknown exactly what effect droperidol has here on the rate of arrhythmia, especially if agitated patients are more likely to experience an arrhythmia than non-agitated patients. This leads to the third question, **"Is droperidol administration associated with an increased risk of arrhythmia among agitated patients?"** Additional data collection is necessary to answer this question. If data were collected showing the rate of arrhythmia among agitated patients is higher when droperidol is not administered than when it is administered, this could be reason to encourage droperidol use for agitated patients in the ED. It is highly recommended to collect data regarding the occurrence of arrhythmia among agitated patients in the ED who did not receive droperidol.

There is not evidence that any of the other variables included in the regression (female, male, age, total administered amount, or vomiting) are associated with the risk of arrhythmia in a patient administered droperidol. To explore whether the legal non-binary designation X or a few of the reasons for droperidol administration (unknown, headache, or abdominal pain) are related to the risk of arrhythmia, we can run a Fisher's Exact Test. We are testing the null hypothesis that any of those variables are independent of arrhythmia occurrence, in particular, that the odds ratio is 1, where the odds ratio (OR) is

$$OR = \frac{\text{odds of arrhythmia among those with the variable of interest}}{\text{odds of arrhythmia among those without the variable of interest}}$$

Refer to Table 3 for the results of the test, which shows that with 95% confidence, headache and arrhythmia occurrence are not independent. The 95% confidence interval for the odds ratio of headache is (0,0.5). Since all values in the confidence interval are less than 1, the risk of arrhythmia is less among patients with a headache than patients without a headache. There is not enough evidence to conclude whether the unknown reason of droperidol administration, abdominal pain, or the legal non-binary designation X is related to the risk of an arrhythmia. This is expected because so few patients that exhibited abdominal pain, had an unknown reason of droperidol administration, or had the legal non-binary designation X as seen in Figures 2 and 3.

5 Inference using QTc

The QTc measurements before droperidol administration were excluded from the logistic regression model because 75.7% of the measurements were missing. However, exploring the relationship between QTc measurements before and after droperidol administration, specifically among agitated patients, could be really informative in understanding the relationship between agitation and arrhythmia in patients that were administered droperidol. This is because higher QTc measurements are clinically known to increase risk of arrhythmia. This leads us to the fourth question, **"Is droperidol administration to agitated patients associated with increased/decreased QTc?"** Observing the trend in QTc measurements before and after droperidol administration could potentially identify how droperidol effects QTc. In particular, if droperidol generally increases QTc, this could be reason (not evidence) to believe that droperidol may be increasing the risk of arrhythmia among agitated patients. If droperidol generally does not increase QTc, or lowers it, this could be reason (not evidence) to believe that droperidol may not be the factor driving the increased risk of arrhythmia among agitated patients. Such analysis should use paired data, i.e. patients with QTc measurements before and after administration of droperidol.

In this dataset, there were 73 patients that received an EKG, meaning they got a QTc measurement, before receiving droperidol, and 91 after being administered droperidol. Only 5 of these observations were paired, meaning only 5 patients had QTc measurements both before and after receiving droperidol. This is not enough observations to do meaningful statistical analysis, however, refer to Figure 4 to see the QTc measurements for these 5 agitated patients before and after they were administered droperidol. For 4 out of the 5 patients, QTc decreased after being administered droperidol. If more data were collected, a paired t-test could be conducted to compare the mean QTc in agitated patients before and after they are administered droperidol. This could show whether droperidol is associated with a change in QTc among agitated patients.

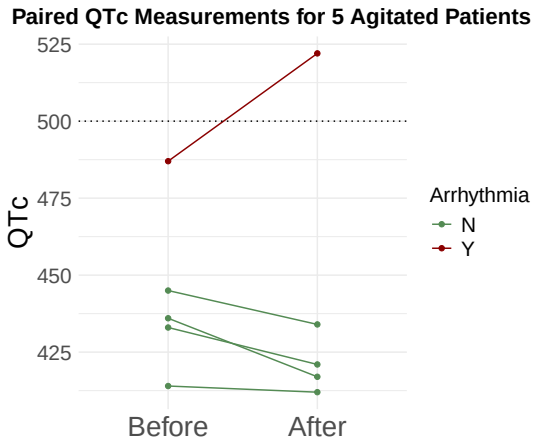

Figure 4: QTc measurements for 5 agitated patients before and after being administered droperidol. The green observations correspond to patients who did not have an arrhythmia, and the red observations correspond to the patient who did have an arrhythmia.

Using paired data is particularly important for comparing the mean QTc before and after administering droperidol because there is likely a fair amount of variation between patient's QTc values. Quantifying the change before and after droperidol administration is the key quantity of interest. It's important to note that of the patients that are able to get paired QTc measurements, the QTc measurement before droperidol is administered may be biased towards lower values. This is because it may not be possible to get QTc measurements before droperidol is administered for severely agitated patients with potentially high QTc.

6 Decision Tree

A decision tree, which would allow practitioners to follow a diagram indicating when droperidol should and should not be given to a patient given their risk of an arrhythmia, would be very practical for clinical use. Unfortunately, the data is severely imbalanced because the occurrence of arrhythmia is so low in this dataset (7%). This low probability event causes classification tree algorithms to always predict *No Arrhythmia*. There are methods to handle data imbalance, such as upsampling from the minority group until the groups are even, downsampling from the majority group, or penalizing more for incorrectly predicting that a patient will not have an arrhythmia when they do (false negative) and penalizing less for incorrectly predicting that a patient will have an arrhythmia when they don't (false positive). While these tricks can result in trees that don't simply always predict *No Arrhythmia*, the trees were very sensitive to the training data and had lots of variation as a result. With the current data, it is not advised to use a decision tree since the reliability of the trees is unclear. Perhaps with more data, a more stable decision tree could be built with high sensitivity.

7 Conclusion

Data collected from the UW Medicine ED between 2022 and 2023 on patients who received the drug droperidol indicates an association between increased arrhythmia and agitation in patients treated with droperidol. However, since agitated patients may have a higher rate of arrhythmia, it is unclear whether droperidol plays a role in this relationship. These data also show an association between decreased arrhythmia and headaches in patients treated with droperidol.

Here we'll address the final question, **"How does a practitioner decide whether or not to administer droperidol to a patient based on their risk of an arrhythmia?"** Ultimately, it is up to UW Medicine to decide whether droperidol use should be allowed for agitated patients in the ED or not given that agitated patients administered droperidol have a higher risk of arrhythmia. If the use of droperidol for relieving agitation in ED patients is prohibited, additional data could potentially be collected on the occurrence of arrhythmia in patients who experience agitation in the ED. This would allow future analysis to be conducted on whether droperidol is associated with an increased risk of arrhythmia among agitated patients, using both the current dataset and the additional data that would be collected.

Alternatively, if droperidol is allowed to be used for agitated patients in the ED, additional data could be collected to identify whether droperidol administration to agitated patients is associated with increased/decreased QTc. This would require recording the QTc measurement for every patient before and after receiving droperidol so that a pairwise comparison could be made to conclude whether droperidol induces QTc prolongation. Unfortunately, this may be impractical since an EKG to record QTc requires a patient to be still, which may not be possible for the severely agitated patients. If any further exploration is done on these data, care must be taken in analyzing the results from the EKG/QTc data since the missingness mechanism is not random due to agitated patients being less likely to receive an EKG/QTc measurement before receiving droperidol. Further analysis could potentially be done with a logistic regression to model what variables can predict QTc prolongation, specifically QTc above 500. However, this model would only be trained on a maximum of 14% of the data since only 91 of 650 patients received an EKG after droperidol administration.

Code to reproduce plots and analysis can be found on Github.