4-14-2020

Gender and Socioeconomic Disparities in Iatrogenic In-Hospital Torsades de Points

Bradley Reinoehl
Western Michigan University, secretbradley117@gmail.com

Gender and Socioeconomic Disparities in Iatrogenic In-Hospital Torsades de Points

Bradley J. Reinoehl

Western Michigan University

Abstract

It has been well established for decades that women are at increased risk for torsades de pointes (TdP). Additionally, it has been well documented that patients of lower socioeconomic status (SES) tend to have inferior health outcomes compared to other patient populations. In this study we investigate the incidence of iatrogenic in-hospital TdP among these two demographic groups. Iatrogenic in-hospital TdP is a complex combination of medical issues and including danger from QT prolonging medications. In theory, a combination of identifiable, demographic risk factors coupled with specific clinical settings could be used to identify patients at high risk for iatrogenic in-hospital TdP. We conducted a retrospective chart review of 457 inpatient electrophysiology consults. Factors reviewed included the presence of TdP, gender, presence of QT prolonging medication, and insurance status (as a marker of SES). Among all patients presenting with TdP (n = 23), female patients experienced a much higher rate than men, as 82.6% ($P < 0.005$) of in-hospital TdP cases were women. When focusing only on medication induced TdP, 83% ($P < 0.005$) of in-hospital TdP cases were women. SES (as measured by insurance status) was also strongly predictive of in-hospital TdP, as 39.1% ($P = 0.01 – 0.005$) of in-hospital TdP cases were in Medicaid/no insurance patients. Our data illustrates a clear female predominance of Iatrogenic in-hospital TdP rates. Regardless of gender, low SES is also a strong predictor of iatrogenic in-hospital TdP. This would suggest an opportunity to identify high risk patients sooner, lowering the rate of iatrogenic in-hospital TdP among these demographics.

Introduction

Torsades de Points (TdP) is a type of ventricular tachycardia, an abnormal heart rhythm, that can lead to sudden cardiac death (Banai et al, 1993). Discovered by François Dessertenne in 1966, it is characterized by a prolonged QT interval on an electrocardiogram (EKG), indicating that ventricular repolarization is not occurring properly (Mitchel, 2017). TdP requires three specific electrocardiographic characteristics for accurate diagnosis; a prolonged QT interval, a slowing or pause prior to the arrhythmia's onset (pause dependence), and its typical polymorphic appearance. "Torsades de Pointes" is French for twisting of the peaks, which describes the arrhythmias characteristic appearance EKGs (Bartos et al, 2016).

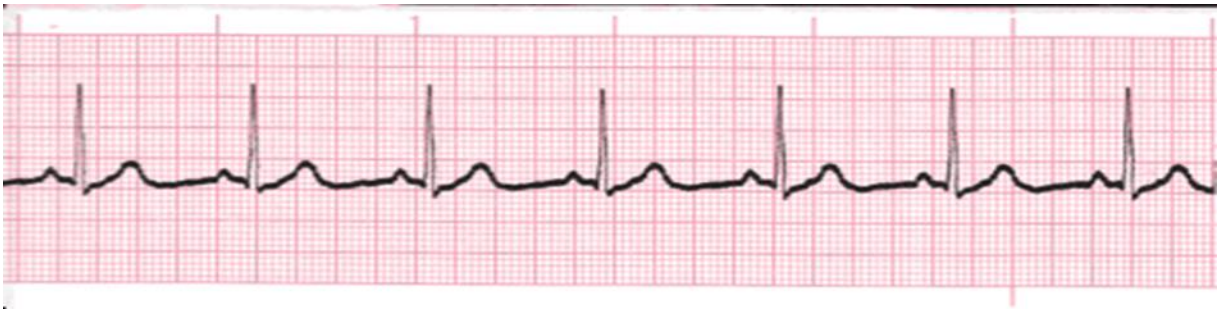

Fig. 1: EKG of a normal heart rhythm. EKG.Academy, [EKG]. Retrieved March 9, 2020 from EKG.Academy: https://ekg.academy/learn-ekg?courseid=318&seq=5. EKG of a normal heart rhythm.

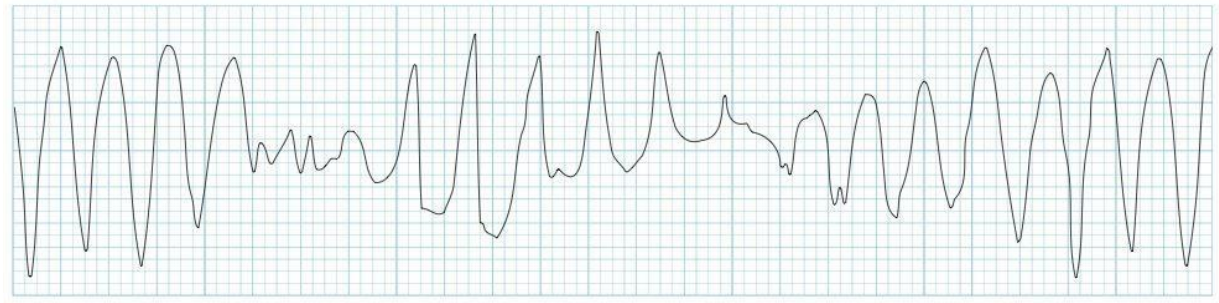

Fig. 2: EKG of a patient with Torsades de Pointes. EmDOCs, [EKG]. Retrieved March 9, 2020 from EmDOCs: http://www.emdocs.net/ecg-pointers-is-it-torsade-de-pointes/.

The essential identifiable risk marker for TdP is QT prolongation. The QT interval represents ventricle myocyte contraction and subsequent repolarization. This critical phase of the cardiac action potential is characterized by a complex series of charged ions flowing across ion channels

embedded in the myocyte's cell membranes. This is best characterized as a four-phase process where first the fast Na+ ion channels open, resulting in myocyte depolarization (Nerbornne, 2005). Once the depolarization reaches a membrane potential of roughly 30 mV, the fast Na^+ receptors are closed, beginning the absolute refractory period. During this period there is an inward flow of Ca^{2+} and an outward flow of K^+. These ion flows offset each other, creating a plateau where the mV remains constant from approximately 200ms. After the plateau, the Ca^{2+} channels are closed, resulting in unopposed outward K+ efflux, returning the cell to its resting potential, where the process is repeated.

There are two major causes of QT prolongation. The first is congenital long QT syndromes (LQTS). These congenital/genetic syndromes are associated with abnormalities in specific potassium and sodium (predominately potassium) ion channels located within myocyte cell membrane. The second are acquired LQTS which are associated with several metabolic abnormalities including hypokalemia, hypomagnesemia and acute myocardial ischemia (Cohagan, 2018). Medications are an important cause of acquired LQTS (Banai et al, 1993). Treatment of Torsades de Points is generally accomplished by avoiding potential offending medications. Implantable pacemakers (to prevent the triggering pause) and defibrillators can be used to prevent/restore normal rhythm to the heart. (Cohagan, 2018).

QT prolongation can be subtle on EKG or telemetry monitoring (or completely unrecognized if no EKG/monitoring is performed) and many commonly used medications may have some effect on the QT interval. There are many different classes of medication that can have can secondarily cause prolonged QT interval. Some of the most classes being antidepressants (amitriptyline, fluoxetine, imipramine, etc…), anesthetics (halothane, propofol), and antibiotics (azithromycin, clarithromycin, erythromycin, ect…) (Jayasinghe 2002). Gender

also plays an important role in Torsades de Pointes in that 70% of all acquired LQTS leading to cardiac arrest occurring in woman (Kawasaki et al. 1998; Makkar, 1993). This due to women's longer baseline QT intervals, increasing their risk for Torsades de Pointes. It is also well established that patients of poorer socioeconomic status (SES) may be more at risk from a clinical misdiagnosis (Schwartz et al, 2014).

Unrecognized medical interactions are an increasingly documented cause of morbidity and mortality among hospitalized patients. One documented concern is the use of medications (alone or in combination) which prolong the QT interval; thus, potentially increasing the risk of TdP (Makkar, 1993). Given the marked disparity in health care exposure seen in certain demographic groups; it could be expected that gender or socioeconomic status may predict in-hospital TdP and sudden death. The purpose of this study will be to investigate this potential discrepancy to determine if a demographic disparity does exist for in-hospital iatrogenic TdP.

Methods

Patient Screening

The study group was made up 457 inpatients that were seen by the electrophysiology service at Bronson hospital for any reason from 2016-2019. Charts were then reviewed by the attending physician where a diagnosis of TdP was confirmed. Specific demographic data was then recovered and analyzed. Screening included confirmation of in-hospital TdP, demographic factors such as gender and SES and presence of potential QT prolonging medication. Additionally, this screening had to be within the Health Insurance Portability and Accountability Act's (HIPAA) guidelines. In order to comply with HIPAA, physicians involved in the study gathered only data

that was essential to the study: identification of TdP, gender, identification of QT prolonging medications, insurance, and pre-existing conditions.

Diagnosis of Torsades de Pointes

Diagnosis of TdP was made through identification of the three electrocardiographic characteristics: pause dependence, QT prolongation, and polymorphic ventricular tachycardia. In figure 3, a post-ectopic pause leads to marked QT prolongation. This is manifest as an abnormal T/U wave. This abnormal repolarization leads to an episode of polymorphic VT (TdP). Abnormal repolarization, with its subsequent prolongation if the QT interval, is the hallmark of TdP. This has many potential causes including genetic disorders, electrolyte abnormalities and various medications. One issue in identification of QT prolongation is the marked overlap between normal and abnormal values. For this reason, we defined a prolonged QT as a value greater than 450 msec. in a male, and 470 msec. in a female. Polymorphic ventricular tachycardia is described as when the QRS complex varies from beat to beat. In TdP this generates the signature "twisting of the points".

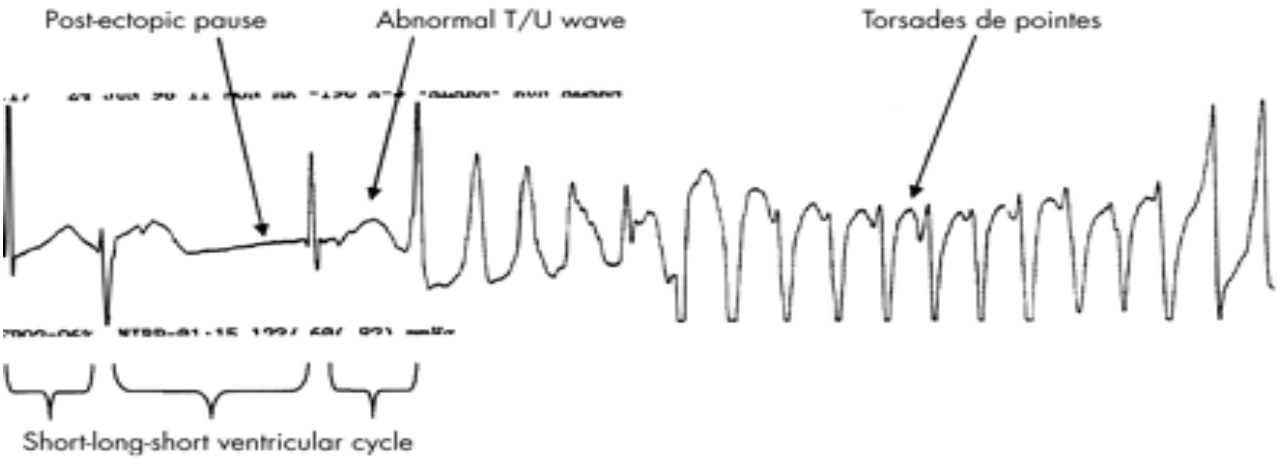

Fig. 3: Breakdown of the diagnosis of TdP based on the EKG. Yap, Y. G., Camm, A. J. (2007). Rhythm strip in a patient with drug induced TdP [EKG]. Retrieved from https://heart.bmj.com/content/89/11/1363

All patients were in-hospital and therefore on telemetry at the time of diagnosis, thus each was diagnosed with the above electrocardiographic findings.

Gender

Genetic females manifest a longer QT interval than genetic males, for this reason, only sex assigned at birth was considered in this study. (Kawasaki, 1998). Lifestyle choice's such as preferred gender should have minimal effect on the individual's phenotype.

QT Prolonging Medications

There is a plethora of medications that have the potential to lengthen QT intervals. In this study, nearly all pharmaceuticals that are associated with Long QT syndrome by the World Health Organization were screened. These drugs can be divided into several different groupings including antihistamines, antibiotics, antipsychotics, antidepressants, and antimigraine drugs (Darpo, 2001). Because the purpose of the study was to identify the magnitude of recognized risk, medications used to treat heart rhythm disorders which are established to prolong the QT interval were excluded.

Insurance

Identifying SES from review of the electronic medical record (EMR) proved to be difficult. The use of medical assistance (Medicaid) or the lack of insurance are recognized as markers of low SES (Casey, 2018). Given the difficulties of working with EMRs, these insurance statuses were the best possible indicator of SES for this study. We do acknowledge that this may not be an accurate measure of SES. This is due to a multitude of factors such a preexisting conditions, disability, and other complex issues.

Pre-Existing Conditions

There are many different conditions that can lead to acquired LQTS and TdP. When needed, a complete reviewed of medical record was performed to identify these conditions. Hypokalemia was one such condition, as low serum levels of potassium delays repolarization, predisposing individuals to long QT syndrome. Congenital Long QT Syndrome was another risk factor screened for, as it predisposes individuals to long QT and subsequently TdP. These were considered in the diagnosis or TdP among our sample population.

Statistics

Several chi squared tests were performed into order to determine the statistical significance of the data. These were performed using the chi squared formula.

$$x^2 = \sum((\text{Observed} - \text{Expected})^2/\text{Expected}) \quad (1)$$

In order to calculate the chi squared value for each variable we also needed to calculate the expected value for each study. This was done by determining the proportion of patients among the screened individuals that were male/female or on Medicare/no insurance. Once these proportions were found, they were applied to the total number of individuals that had in-hospital TdP to determine the expected value of the expected demographic group. Additionally, the degrees of freedom were needed for every individual chi squared test. This was done using the formula for degrees of freedom.

$$df = n - 1 \quad (2)$$

Once calculated, the degrees of freedom and the chi squared value were used to find a p value with the chi squared table. For this study, a standard p value of $p \leq 0.05$ was used to determine significance.

Adherence to HIPAA protocol

Several different protocols were followed to ensure HIPAA regulations were met. All information collected by electrophysiologists was on their own patients, which was then complied into a format in which all Protected Health Information (PHI) was removed per HIPPA guidelines. This included names, patient identification numbers, dates, geographic information, and any other possible methods to identify the patient involved (HIPPA Journal, 2019). After ensuring the only information being presented was gender, medications, insurance and compounding conditions, the data was curated and analyzed by myself. It is through this method that all HIPPA protocols were followed.

Results

Analysis of patient records was done to observe the presence of TdP, gender, potential QT prolonging medications and insurance status (Medicare/private insurance vs. Medicaid/no insurance). Women made up 82.6% of all TdP consults. When considering woman represented only 34.8% of total consults performed, female sex was a statistically significant predictor of in hospital TdP ($p < 0.005$). When considering only TdP patients triggered by QT prolonging medications, 83.3% were women. Again, confirming a strong statistical prevalence of medication induced TdP in women ($p < 0.005$). The last variable tested was the incidence of in-hospital TdP correlated with Medicaid/no insurance.

The total percentage of patients with Medicaid/no insurance was 39% of all TdP consults. When considering this group of patients represented only 15.3% of total consults performed, SES, as defined by insurance status, was a statistically significant predictor of in hospital TdP ($p = 0.01 – 0.005$).

Total Patents	457
Male	298
Female	159

Table 2. Table illustrates the total number of consult patients reviewed, as well as their breakdown by sex.

Primary Payor	2017	2017 Prop.	2018	2018 Prop	R2019	R2019 Prop.
BCBS	2,216	13%	2,300	13%	2,275	13%
Medicare	9,934	58%	9,929	58%	10,071	58%
Medicaid	2,595	15%	2,659	15%	2,675	15%
Other Comm.	2,096	12%	1,845	11%	1,667	10%
All Other*	260	2%	466	3%	673	4%
Grand Total	17,101	100%	17,199	100%	17,361	100%

Table 3. MIDB, State Data Analysis of insurance status, 2017-R2019, R2019=Oct'18-Sept'19, BMH, Adults Only (18+), excludes Normal Newborns & Obstetrics Service Lines.

Patient number	Gender	QT Prolonging Medication	Insurance (Medicaid/No Insurance)	Pre-Existing Conditions
1	F	Y	N	
2	F	Y	N	
3	F	Y	Y	
4	F	N	N	
5	M	N	N	
6	F	Y	Y	Hypokalemia, HD
7	M	N	N	
8	F	Y	N	Congenital LQTS
9	F	Y	N	
10	F	Y	N	
11	F	Y	N	
12	F	Y	N	
13	F	Y	Y	
14	F	Y	N	
15	F	Y	Y	
16	M	Y	N	
17	F	N	Y	Supplements
18	F	N	Y	
19	F	Y	Y	
20	F	Y	N	
21	M	Y	Y	
22	F	Y	Y	
23	F	N	N	VT and TdP

Table 1. All in-hospital TdP patients that were reviewed from consults, with demographic breakdown by gender, medication, and insurance.

Discussion

After analysis of the data, it was found that female patients were significantly more likely to experience in-hospital TdP then their male counterparts. This result remained equally significant when only QT prolonging medications were considered. This indicates that drug induced, in-hospital TdP is more frequent in women than men. Additionally, insurance status (Medicaid/no insurance) was also a significant predictor of in-hospital TdP. This would suggest a correlation between SES and incidence of in-hospital TdP.

Gender's impact on the incidence of TdP is well documented in the literature, with female gender being known as a risk factor (Kawasaki, 1998; Makkar, 1993). In this review, the prevalence of in-hospital, drug induced TdP was significantly higher in women than men. This adds additional confirmation to genders role in risk of TdP. Despite this well documented risk, female gender remains a strong predictor of adverse outcomes. The cause of this gender discrepancy remains complex and multidimensional. One potential factor is missed screening opportunities for woman when potential QT prolonging drugs are required. Focused screening, while ultimately reducing risk, is not consistently performed. More consistent screening would reduce higher risk patient's exposure to QT prolonging medications. Another possible cause is the unrecognized QT prolonging potential of many medications. Older medications are predominantly the cause of this, as often they excluded or underrepresented women in their testing pools (Liu et al. 2016). This in turn causes many older medications to have unforeseen, effects on women such as prolonging the QT interval.

Several potential strategies could be implemented, separately or together, to combat this gender discrepancy. One such plan would be a Continuing Medical Education (CME) program to further educate physicians about gender as a risk factor for TdP. This plan is likely the easiest to

implement, as these programs already exist and could easily be accommodate a portion of their curriculum to these disparities. This would help explain not only why women have increased risk but also would help with avoiding potential QT prolonging medications. Another prevention method possible would be to require new testing on all older medications tested without/underrepresenting women. Several modern studies on older medications, considering proper participant demographics, and found unaccounted risk factors (Reinoehl et al. 1996). A uniform testing of all older drugs still in use would help identity the risk factors of common pharmaceuticals. This would allow physicians to make more informed choices when prescribing medication to women and reducing the risk for iatrogenic TdP. One final method to reduce rates in iatrogenic in-hospital TdP would be the screening of all at risk individuals (gender and SES). Focused screening within a population is never simple, as issues such as cost and marginal benefit create challenges. However, in-hospital TdP had conditions that may offset these normally heavy burdens. EKGs are relatively inexpensive and offer a wide range of marginal benefit (such as advance testing for other rhythm abnormalities). For these reasons, focused screening of individuals with baseline EKG should be performed on all patients to decrease the incidence of in-hospital TdP. It's through a combination of these three strategies that information about prescription drugs' effect on women could be quickly identified large proportion of physicians. Emphasizing the risk of potential QT prolonging medications, demographic factors, and screening procedures could efficiently be done using electronic medical records (EMR). Through use of alerts and access to information, physicians would be better equipped to screen patients for TdP risk factors.

Our findings would indicate that poor SES is a risk factor for iatrogenic in-hospital TdP. This phenomenon likely traces back to three root issues, access to care, substandard care and

mistrust of the patient-doctor relationship (Burstin et al. 1992). Access to care is likely an indirect cause of iatrogenic TdP. Poor access to care directly leads to delay diagnosis and disease progression. This more advanced disease would likely require more aggressive therapy. For this reason, patients with worse access to care generally face more precarious health outcomes. Increasing the chance of being prescribed high risk medications. Patient-doctor relationships have become an important and prominent field of study over the last decade. It has been found that these relationships can vary greatly due to different demographic factors, with SES being the quintessential example (Davis, 1968; Epstein et al. 1985). Less effective communication between doctors and patients of lower SES can be risk factor for medical misdiagnosis due to misunderstandings. In the landscape of iatrogenic TdP, this means many symptoms, such as cold sweats, chest pain, and shortness of breath could be overlooked (Li et al. 2017). Substandard care is an unfortunate reality that plagues the medical system for individuals of lower SES (Schwartz et al, 2014). This can manifest in many ways, such as misdiagnosis or medical mistakes. In the case of iatrogenic TdP, this could potentially cause medications that can prolong the QT interval to be prescribed to at risk individuals. While there are surely numerous, subtle aspects to SES and its relation to TdP, more research is needed before any conclusions formed.

Additionally, it should be noted that insurance status is not a reliable indicator of SES; however, for electronic medical records it is accepted as a standard measurement (Casey et al. 2018). This could lead to misleading data. Therefore, a prospective study using more direct SES indicators such as income would be advised to further analyze this aspect of the study.

Overhauling the medical system to rid it of these disparities has been a popular topic over the last two decades. Some of the most common opinions on the matter are to host lectures for physicians regarding inclusivity and training a more diverse roster of physicians for the future.

Hosting lectures in medical schools and post-doctorate CMEs have shown to help physicians better communicate to wider groups of individuals (Riesenberg et al. 2019). Better communication helps to improve the patient-doctor relationship and potentially reduces of subpar care. This in turn reduces the rates of both misdiagnosis and medical mistakes. Despite their effectiveness, the most effective way to cut down on healthcare disparities is to train a more diverse cast of physicians (Nickens et al, 2001). It is critical to have diversity across all aspects of life, SES included, among physicians. Undoubtedly, this will help improve patient-doctor relationships and bring down rates of misdiagnosis/medical mistakes, reducing iatrogenic in-hospital TdP for those of lower SES.

Conclusion

Iatrogenic in-hospital TdP is a complex issue with many different risk factors making it difficult to recognize. Two of these risk factors are female gender and low SES. This offers the potential for improved recognition of risk through physician education, further drug research, and physician diversification. Using these, it would be possible to recognize these high-risk individuals earlier, avoiding potential life threatening consequences.

References

Banai, S., & Tzivoni, D. (1993, April). Drug therapy for torsade de pointes. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8269292

Bartos, D. C., Grandi, E., & Ripplinger, C. M. (2016, July 1). Ion Channels in the Heart. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516287/

Burstin H. R., Lipsitz S. R, Brennan T.A. (November 4, 1992) Socioeconomic Status and Risk for Substandard Medical Care. JAMA. 1992;268(17):2383–2387. doi:10.1001/jama.1992.03490170055025

Casey, J. A., Pollak, J., Glymour, M. M., Mayeda, E. R., Hirsch, A. G., & Schwartz, B. S. (2018). Measures of SES for Electronic Health Record-based Research. American Journal of Preventive Medicine, 54(3), 430–439. doi: 10.1016/j.amepre.2017.10.004

Cohagan, B. (2018, September 21). Torsade de Pointes. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK459388/

Darpo B. (2001). Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. Eur Heart J Supplements. Retrieved from http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.498.1264&rep=rep1&type=pdf

Davis, M. (1968). Physiologic, Psychological and Demographic Factors in Patient Compliance with Doctors' Orders. Medical Care, 6(2), 115-122. Retrieved March 16, 2020, from www.jstor.org/stable/3763070

EKG.Academy. [EKG photograph]. Retrieved from https://ekg.academy/learn-ekg?courseid=318&seq=5

EmDocs. (2018, June 13). [EKG photograph]. Retrieved from http://www.emdocs.net/ecg-pointers-is-it-torsade-de-pointes/

Epstein, A. M., Taylor, W. C., & Seage, G. R. (1985). Effects of patients socioeconomic status and physicians training and practice on patient-doctor communication. The American Journal of Medicine, 78(1), 101–106. doi: 10.1016/0002-9343(85)90469-3

HIPAA Journal. (2019, March 7). What is Considered Protected Health Information Under HIPAA? Retrieved from https://www.hipaajournal.com/what-is-considered-protected-health-information-under-hipaa/

Jayasinghe, R., Kovoor, P. (May 1, 2002). Drugs and the QTc interval. Retrieved from https://www.nps.org.au/australian-prescriber/articles/drugs-and-the-qtc-interval

Kawasaki, R., Machado, C., Reinoehl, J., Fromm, B., Baga, J. J., Steinman, R. T., & Lehmann, M. H. (1995). Increased Propensity of Women to Develop Torsades de Pointes During Complete Heart Block. Journal of Cardiovascular Electrophysiology, 6(11), 1032–1038. doi: 10.1111/j.1540-8167.1995.tb00380.x

Kinsinger, F. S. (2009, December). Beneficence and the professional's moral imperative. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342811/

Li, M., & Ramos, L. G. (2017). Drug-Induced QT Prolongation And Torsades de Pointes. P & T : a peer-reviewed journal for formulary management, 42(7), 473–477.

Liu, K. A., & Mager, N. A. D. (2016). Women's involvement in clinical trials: historical perspective and future implications. *Pharmacy Practice*, *14*(1), 708–708. doi: 10.18549/pharmpract.2016.01.708

Makkar, R. R., Fromm, B. S., Steinman, R. T., Meissner, M. D., Lehmann, M. H. (December 1, 1993). Female Gender as a Risk Factor for Torsades de Pointes Associated with Cardiovascular Drugs. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/8230644

Mitchel, B. L. (2017, September). Long QT Syndrome and Torsades de Pointes Ventricular Tachycardia - Cardiovascular Disorders. Retrieved from https://www.merckmanuals.com/professional/cardiovascular-disorders/arrhythmias-and-conduction-disorders/long-qt-syndrome-and-torsades-de-pointes-ventricular-tachycardia

Nerbornne, J. M., Kass, R. S. (October 1, 2005). Molecular Physiology of Cardiac Repolarization. Retrieved from: https://journals.physiology.org/doi/full/10.1152/physrev.00002.2005?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Nickens, H. W., Smedley, B. D. (2001). The right thing to do, the smart thing to do: enhancing diversity in the health professions: summary of the Symposium on Diversity in Health Professions in honor of Herbert W. Nickens, M.D. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK223632/

Reinoehl, J., Frankovich, D., Machado, C., Kawasaki, R., Baga, J. J., Pires, L. A., … Lehmann, M. H. (1996). Probucol-associated tachyarrhythmic events and QT prolongation: Importance of gender. American Heart Journal, 131(6), 1184–1191. doi: 10.1016/s0002-8703(96)90095-2

Riesenberg, L. A., Leitzsch, J., Massucci, J. L., Jaeger, J., Rosenfeld, J. C., Patow, C., … Karpovich, K. P. (2009). Residents' and Attending Physicians' Handoffs: A Systematic Review of the Literature. Academic Medicine, 84(12), 1775–1787. doi: 10.1097/acm.0b013e3181bf51a6

Schwartz, R. C., & Blankenship, D. M. (2014, December). Racial disparities in psychotic disorder diagnosis: A review of empirical literature. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4274585/

Yap, Y. G., Camm, A. J. (2007). Rhythm strip in a patient with drug induced TdP [EKG]. Retrieved from https://heart.bmj.com/content/89/11/1363