

Torsades de Pointes induced by Methadone and Clonazepam Use

Anthony G. Ashkar, Tamara Goldberg, Pharm.D., Alina Masters, MD, Ilir Maraj, MD,
and Samy I. McFarlane
SUNY Downstate and Kings County Hospital Centers, Brooklyn New York, USA 11203

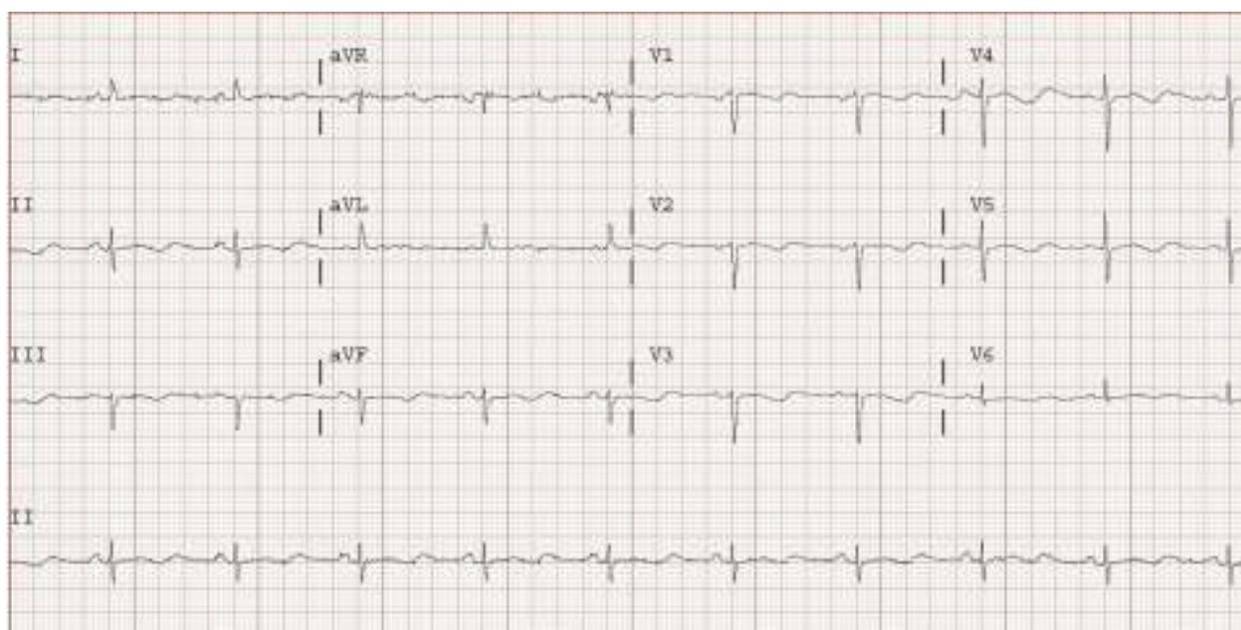
Address and correspondence :

Samy I. McFarlane, MD, MPH, MBA, FACP
Professor of Medicine and Endocrinology
State University of New York-Downstate Medical Center
450 Clarkson Avenue, Box 50
Brooklyn, New York, 11203
Tel: 718-270-3711
Fax: 718-270-6358

Background: Although a recent study by Proctor SL, et al. showed that illicit drug use rates at six months of treatment with either methadone or buprenorphine were comparable among patients ⁽¹⁰⁾ and another study by Madlung-Kratzer, et al. showed that slow-release oral morphine was not inferior to methadone as detoxification treatment ⁽⁷⁾, methadone continues to be commonly prescribed in drug addiction centers ⁽¹¹⁾. The compound was developed in Germany in 1937, by scientists who sought to solve Germany's longstanding opioid shortage and derive a synthetic opium from readily available precursors ⁽¹⁾. According to the most recent CDC statistics, between the period of 1999 to 2006, the number of deaths from opioid pain relievers more than tripled in the U.S., from 4,000 to 13,800. Of these, deaths from methadone overdose during this time period increased from 790 to 5,420 individuals. Methadone was involved in approximately one in three opioid-related overdose deaths ⁽¹²⁾. This medication has been implicated in prolongation of the QT interval which may predispose to Torsades de Pointes, a fatal cardiac arrhythmia. The mechanism of QT prolongation by methadone, is thought to be the result of inhibition of the hERG K⁺ channel ⁽³⁾. Additionally, methadone blocks Na⁺ channels, and this blockade compensates for hERG K⁺ inhibition by methadone resulting in diminished risk of Torsades by this agent. Benzodiazepines have been shown to reverse the methadone induced Na⁺ channel blockade, thus resulting in action potential prolongation by intensifying methadone-induced hERG channel inhibition and potentiating methadone's ability to induce Torsades De Pointes ⁽⁶⁾. In addition, Peles, et al. showed that QT prolongation was greater among patients on methadone who also had a positive urine test for benzodiazepines ⁽⁹⁾⁽¹³⁾.

Objective: To report a case of Torsades de Pointes associated with Methadone prescription.

Report: This case is presented anonymously without any patient identifiers. A 59-year-old woman with a history of polysubstance abuse presented to the ER complaining of dizziness, lightheadedness and near-syncope. Patient's home medication list included Methadone 190 mg prescribed by her outpatient drug rehabilitation center beginning six months ago as well as aspirin, albuterol and cingulair, for unknown duration and with unknown compliance. Patient had a history of crack cocaine abuse and heroin abuse but did not have any history of alcohol use, and she reported no significant family history of sudden cardiac death. Her initial EKG on admission showed a prolonged QT interval of 540 with QTc of 512. See figure below.



She was placed on continuous cardiac monitoring to evaluate for arrhythmia and her pre-syncope work-up included a fingerstick glucose, CBC, serial EKGs, cardiac enzymes and a transthoracic echocardiogram. Patient's usual dose of methadone was decreased by half; it wasn't completely held because patient was clinically dependent on her methadone and to avoid withdrawal symptoms. Patient's electrolytes, including potassium, magnesium and calcium were all within normal limits. After three days of monitoring with negative work-up, she was planned for discharge, however cardiac telemetry revealed polymorphic ventricular tachycardia. See figure below.



The telemetry strip above demonstrates *Torsade de Pointes*, which literally means a "twisting of the spikes". The rhythm is a polymorphic ventricular tachycardia with a distinctive twisting of the QRS complex around the isoelectric baseline. This rhythm can rapidly degenerate into ventricular fibrillation and resultant cardiac arrest in the absence of immediate medical intervention.

Our patient remained hemodynamically stable and at this point only complained of lightheadedness. She was given 2 grams IV Magnesium Sulfate STAT with conversion of the rhythm to bigeminy. Patient was transferred to CCU and received an emergent transvenous pacemaker. See figure below.



Further history obtained at the bedside indicated that the patient also had consumed an unknown amount of non-prescribed clonazepam provided by a visitor in addition to hospital-provided methadone. The combined QT prolongation effects of methadone coupled with benzodiazepines had led to a potentially fatal arrhythmia.

Before discharge, our patient was educated on the risks of continuing benzodiazepine use especially while taking methadone. Proper follow up was scheduled for her and she was discharged with half her usual dose of methadone, with normalization of her QT interval on EKG.

Review of literature:

First reports of methadone-induced Torsades de Pointes were described in 17 patients back in 2002⁽⁴⁾. These initial cases were associated with high dose methadone therapy and resulted in heightened awareness of this adverse drug reaction among clinicians. Subsequently, a boxed warning was added to FDA labeling for methadone in 2006 about arrhythmia risk, followed by publication of clinical practice guidelines in 2009 recommending QTc interval screenings. Kao and colleagues have published the incidence of methadone QT prolongation from the FDA Adverse Events Reporting System (FAERS) database between 1997 and 2011. They found 379 cases of methadone related QTc prolongation or torsades in that time period. This study also reported an 11.1% attributable mortality due to Torsades related to methadone⁽²⁾. Previous studies have shown a positive correlation between both serum concentration of methadone and length of methadone use with the QT interval length⁽⁵⁾⁽⁸⁾.

Conclusion and Lessons Learned:

Methadone is known to prolong the QT interval and has the potential to trigger Torsades de Pointes, particularly if simultaneously administered with prescribed or non-prescribed drugs that also prolong the QT interval. Physicians are encouraged to obtain routine EKG studies on patients who are on methadone prior to prescribing additional agents with QT prolongation potential. Prolongation of the absolute QT interval beyond 500 msec is commonly considered to confer an increased risk for arrhythmia development. Established risk factors which can predispose to Torsades de Pointes include female gender, hypokalemia, bradycardia, congestive heart failure, ion-channel polymorphisms and baseline QT prolongation (Table 1)⁽¹⁴⁾. Our patient had normal ejection fraction, electrolytes within normal limits, and no family history of sudden cardiac death; however, we were unable to obtain a baseline EKG prior to initiation of methadone. Patient education regarding the potentially fatal nature of the arrhythmia when taking methadone is of paramount importance, particularly with the increasing use of methadone in drug-rehabilitation centers as well as the number of methadone-related overdoses and deaths. This case also highlights the need to consider non-prescribed medications ingested by patients with known drug addiction history that might confound the clinical presentation and lead to serious consequences.

Risk Factors for Drug-Induced Torsade de Pointes

- Female Sex
- Hypokalemia
- Bradycardia
- Congestive Heart Failure
- Severe Hypomagnesemia
- Ion-Channel Polymorphisms
- Baseline QT Prolongation

References:

¹ Bockmuhl, M. Über eine neue Klasse von analgetisch wirkenden Verbindungen Ann. Chem. 561, 52 (1948)

² Kao D, et al. Trends in Reporting Methadone-Associated Cardiac Arrhythmia, 1997–2011: An Analysis of Registry Data. Ann Intern Med. 2013 May 21; 158(10): 735–740

³ Katchman AN, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K⁺ currents. J Pharmacol Exp Ther. 2002;303:688–694.

- ⁴ Krantz MJ, et al. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med.* 2002 Sep 17;137(6):501-4.
- ⁵ Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. *Pharmacotherapy.* 2005;25:1523–1529
- ⁶ Kuryshv Y.A., et al. (2010) Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. *J Cardiovasc Pharmacol* 56: 420–430 [[PubMed](#)]
- ⁷ Madlung-Kratzer, et al. A double-blind, randomized, parallel group study to compare the efficacy, safety and tolerability of slow-release oral morphine versus methadone in opioid-dependent in-patients willing to undergo detoxification. *Addiction.* 2009 Sep;104(9):1549-57. doi: 10.1111/j.1360-0443.2009.02653.x.
- ⁸ Martell BA, et al. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol.* 2005 Apr 1;95(7):915-8.
- ⁹ Peles, et al. Prospective study of QTc changes among former opiate addicts since admission to methadone maintenance treatment: benzodiazepine risk. *J Addict Med.* 2013 Nov-Dec; 7(6): 428-34. doi: 10.1097/ADM.0b013e3182a8a4f2.
- ¹⁰ Proctor SL., et al. A naturalistic comparison of the effectiveness of methadone and two sublingual formulations of buprenorphine on maintenance treatment outcomes: Findings from a retrospective multisite study. *Exp Clin Psychopharmacol.* 2014 Oct;22(5):424-33. doi: 10.1037/a0037550. Epub 2014 Jul 28.
- ¹¹ Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva: World Health Organization; 2009. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK143185/>
- ¹² Prescription Painkiller Overdoses: Methadone. <http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/>
- ¹³ <http://www.ehealthme.com/ds/clonazepam/electrocardiogram+qt+prolonged-> accessed on 10/06/14
- ¹⁴ Yap, Yee Guan, et al. Drug Induced QT Prolongation and Torsades de Pointes. *Heart* 2003;89:1363–1372