



QT Prolongation and Psychotropic Medications

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INTRODUCTION

Prolongation of the QT interval, which may predispose to ventricular arrhythmia, remains an important problem for psychiatrists and other clinicians. QT prolongation is associated with fatal ventricular arrhythmias such as Torsades de Pointes (TdP), especially in those with medical illness (1). Antipsychotic drugs can cause serious cardiovascular side effects such as arrhythmia, cardiomyopathy, and myocarditis (2). QT interval prolongation is the most common rhythm disorder that can lead to TdP. TdP can transform into ventricular fibrillation, causing sudden death. Drug-induced QT prolongation is more common in women than men (3). Predisposing factors such as hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, malnutrition, advanced age, female gender, diabetes mellitus, cerebrovascular disease, coronary heart disease, hypertension, congestive heart failure, hypothermia, hypoglycemia, obesity and hypothyroidism may cause QT prolongation (4). The mean QTc interval in healthy individuals is 400 ms, and the longer the interval, the greater the risk of TdP. The fact that the QTc range is greater than 500 ms is an important risk factor for TdP (2,3). QTc is a normal upper limit of 450 ms in men and 460 ms in women (5).

ANTIPSYCHOTIC MEDICATIONS

Typical Antipsychotic Medications

Studies have noted that typical antipsychotic drugs cause greater QT prolongation than atypical antipsychotic drugs. In a study using psychotropic drugs and

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be the first choice for individuals with cardiac risk factors who have not taken antidepressants before. Clinicians should approach the decision to prescribe a psychotropic known to be at risk of QTc interval prolongation using a comprehensive risk-benefit analysis, including the risk of onset QTc, comorbid conditions, and whether or not to adequately treat existing psychopathology (25,40).

REFERENCES

1. Malik M., Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug safety*. 2001; 24, 323-351. doi.org/10.2165/00002018-200124050-00001
2. Stöllberger C, Huber JO, Finsterer J, et al. Antipsychotic drugs and QT prolongation. *International clinical psychopharmacology*. 2005; 20(5), 243-251. doi: 10.1097/01.yic.0000166405.49473.70
3. Roden DM. Drug-induced prolongation of the QT interval. *New England Journal of Medicine*. 2004; 350(10), 1013-1022. doi: 10.1056/NEJMra032426
4. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2003; 23(7), 881-908. doi.org/10.1592/phco.23.7.881.32730
5. Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation*. 1992; 85(1 Suppl), I140-144.
6. Carrà G, Crocamo C, Bartoli F, et al. First-generation antipsychotics and QTc: any role for mediating variables? *Human Psychopharmacology: Clinical and Experimental*. 2016; 31(4), 313-318. doi.org/10.1002/hup.2540
7. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *Journal of the American Heart Association*. 2015;4(2). doi.org/10.1161/JAHA.114.001568
8. Sanguinetti MC, Jiang C, Curran ME, et al. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel *Cell Find this article online*. 1995; 81: 299-307. doi.org/10.1016/0092-8674(95)90340-2
9. Tracz K, Owczuk R. Small doses of droperidol do not present relevant torsadogenic actions: a double-blind, ondansetron-controlled study. *Clinical pharmacology in drug development*. 2015;79(4):669-76. doi.org/10.1111/bcp.12527
10. Beach SR, Celano CM, Sugrue AM, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018; 59(2), 105-122. doi.org/10.1016/j.psym.2017.10.009
11. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*. 2013; 382(9896), 951-962. doi.org/10.1016/S0140-6736(13)60733-3
12. Ozeki Y, Fujii K, Kurimoto N, et al. QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010; 34(2), 401-405. https://doi.org/10.1016/j.pnpbp.2010.01.008
13. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *Journal of clinical psychopharmacology*. 2004; 24(1), 62-69. doi: 10.1097/01.jcp.0000104913.75206.62
14. Polewiartek C, Sneider B, Graff C, et al. The cardiac safety of aripiprazole treatment in patients at high risk for torsade: a systematic review with a meta-analytic approach. *Psychopharmacology*.

- logy (Berl). 2015;232(18):3297-308. doi.org/10.1007/s00213-015-4024-9
15. Potkin SG, Preskorn S, Hochfeld M, et al. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *Journal of clinical psychopharmacology*. 2013;33(1):3-10. doi: 10.1097/JCP.0b013e31827c0314
 16. Goff DC, McEvoy JP, Citrome L, et al. High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. *Journal of clinical psychopharmacology*. 2013;33(4):485-90. doi: 10.1097/JCP.0b013e3182977308
 17. Leonard CE, Freeman CP, Newcomb CW, et al. Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States. *Journal of clinical & experimental cardiology*(6). 2013;Suppl 10(6):1-9 doi: 10.4172/2155-9880.S10-006
 18. Nykamp DL, Blackmon CL, Schmidt PE, et al. QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine *Annals of Pharmacotherapy*. 2005;39(3):543-6. doi.org/10.1345/aph.1E513
 19. Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. *Journal of clinical psychopharmacology*. 2001; 21(1), 8-13. doi: 10.1097/JCP.0b013e3182977308
 20. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *Bmj*. 2002; 325(7372), 1070. doi.org/10.1136/bmj.325.7372.1070
 21. Gil FP, Grohmann R, Rürher E, et al. Asymptomatic bradycardia associated with amisulpride. *Pharmacopsychiatry*. 2001; 34(06), 259-261. doi: 10.1055/s-2001-18033
 22. Desta Z, Kerbusch T, Flockhart DA, et al. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clinical Pharmacology & Therapeutics*. 1999 65(1), 10-20. doi.org/10.1016/S0009-9236(99)70117-7
 23. Liu BA & Juurlink DN. Drugs and the QT interval—caveat doctor. *New England Journal of Medicine*. 2004; 351(11), 1053-1056. doi: 10.1056/NEJMmp048192
 24. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *Bmj*. 2013;346:f288. doi: 10.1136/bmj.f288
 25. Girardin FR, Gex-Fabry M, Berney P, et al. Drug-induced long QT in adult psychiatric inpatients: the 5-year cross-sectional ECG Screening Outcome in Psychiatry study. *American Journal of Psychiatry*. 2013;170(12):1468-76. Doi: 10.1176/appi.ajp.2013.12060860
 26. Hasnain M, Howland RH, Vieweg WV. Escitalopram and QTc prolongation. *Journal of Psychiatry & Neuroscience*. 2013;38(4):E11. doi: 10.1503/jpn.130055
 27. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *The Journal of Clinical Psychiatry*. 2014;75(5):e441-9. Doi: 10.4088/JCP.13r08672
 28. Schreffler SM, Marraffa JM, Stork CM, et al. Sodium channel blockade with QRS widening after an escitalopram overdose. *Pediatric Emergency Care*. 2013;29(9):998-1001. doi: 10.1097/PEC.0b013e3182a314b7
 29. Ray WA, Chung CP, Murray KT, et al. High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death. *The Journal of Clinical Psychiatry*. 2016. doi: 10.4088/JCP.15m10324.
 30. Spindelegger CJ, Papageorgiou K, Grohmann R, et al. Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. *International journal of neuropsychopharmacology*. 2014;18(4). doi.org/10.1093/ijnp/pyu080

31. Brzozowska A, Werner B: Observation of QTc prolongation in an adolescent girl during fluvoxamine pharmacotherapy. *Journal of child and adolescent psychopharmacology*. 2009;19(5):591-2. doi: 10.1089/cap.2008.0136
32. Jasiak NM, Bostwick JR. Risk of QT/QTc prolongation among newer non-SSRI antidepressants. *Annals of Pharmacotherapy*. 2014;48(12):1620-8. Doi: 10.1177/1060028014550645
33. Maljuric NM, Noordam R, Aarts N, et al. Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. *British journal of clinical pharmacology*. 2015;80(4):698-705. DOI: 10.1111/bcp.12681
34. Berling I, Isbister GK. Mirtazapine overdose is unlikely to cause major toxicity. *Clinical Toxicology*. 2014;52(1):20-4. DOI: 10.3109/15563650.2013.859264
35. Leonard CE, Bilker WB, Newcomb C, et al. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiology and drug safety*. 2011;20(9):903-13. DOI: 10.1002/pds.2181
36. Citrome L. Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practice*. 2015;69(9):978-97. DOI: 10.1111/ijcp.12714
37. Wang Y, Nomikos GG, Karim A, et al. Effect of Vortioxetine on Cardiac Repolarization in Healthy Adult Male Subjects: Results of a Thorough QT/QTc Study. *Clinical pharmacology in drug development*. 2013;2(4):298-309. DOI: 10.1002/cpdd.51
38. Noordam R, van den Berg ME, Niemeijer MN, et al. Assessing Prolongation of the Heart Rate Corrected QT Interval in Users of Tricyclic Antidepressants: Advice to Use Fridericia Rather Than Bazett's Correction. *Journal of clinical psychopharmacology*. 2015;35(3):260-5 DOI: 10.1097/JCP.00000000000000321
39. Neuman G, Shehadeh N, Pillar G. Unsuccessful suicide attempt of a 15 year old adolescent with ingestion of 5000 mg modafinil. *Journal of clinical sleep medicine*. 2009;5(4):372-3. doi.org/10.5664/jcsm.27550
40. Funk MC, Beach SR, Bostwick JR, et al. QTc prolongation and psychotropic medications. *American Journal of Psychiatry*. 2020; 177(3), 273-274. Doi: 10.1176/appi.ajp.2019.1760501
41. Girardin FR, Gex-Fabry M, Berney P, et al. Drug-induced long QT in adult psychiatric inpatients: the 5-year cross-sectional ECG Screening Outcome in Psychiatry study. *American Journal of Psychiatry*. 2013;170(12):1468-76. Doi: 10.1176/appi.ajp.2013.12060860
42. Lin CH, Chen CH, Wang SY, et al. Predictive factors for QTc prolongation in schizophrenic patients taking antipsychotics. *Journal of the Formosan Medical Association= Taiwan yi zhi*. 2004; 103(6), 437-441.
43. Thomas D, Wu K, Kathöfer S, et al. The antipsychotic drug chlorpromazine inhibits HERG potassium channels. *British journal of pharmacology*. 2003; 139(3), 567-574. doi.org/10.1038/sj.bjp.0705283