Vortioxetine: A Safe Treatment for Depression in a Medically Complex Patient With QTc Prolongation

Chelsea Eisenach, MD[1]; Sean Lynch, MD[1]; Seema Quraishi, MD[1]

1- Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, Department of Psychiatry

Background

- Depression is a prevalent illness in the general population, with a lifetime risk of 15% and point prevalence of 5%.[1]
- In medically ill patients, the prevalence of depression increases to 27%.[1]
- Depression has further been linked to poorer health outcomes and is the major cause of disability worldwide.[2]
- The Montgomery-Åsberg Depression Rating Scale (MADRS) has been widely validated to assess severity of depression in patients who have been clinically diagnosed.[5]
- Serotoninergic agents, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are the gold standard for treatment of depression.[1]
- Providers must be aware of drug-drug interactions, particularly for medically ill patients, who are at greater risk for adverse events and lower tolerability.[1]
- Prolongation of the corrected QT (QTc) interval on electrocardiograms (ECGs) is a potential adverse effect of many antidepressants, and places patients at increased risk for Torsades de Pointes and sudden cardiac death.[3]
- Patients are at increased risk for cardiac events when the QTc is greater than 500ms.[3]
- SSRIs/SNRIs are thought to prolong the QTc interval in a dose-dependent manner by blocking the inward-rectifying potassium channels.[10,11]
- Tricyclic antidepressants (TCAs) are known to have greater propensity for elongating QTc. While SSRIs are generally safer, citalopram has been noted to have the greatest risk in the class for prolonging QTc, while others including sertraline are generally considered safe.[4]
- Several newer agents with novel mechanisms of action have been approved in recent years for treatment of depression; their safety profiles are less well established.

Vortioxetine

- Vortioxetine has been approved for treatment of depression in adults since 2013.[6]
- It has a novel mechanism of action, with antagonism of the 5HT3, 5HT1D, and 5HT7 receptors, partial agonism of the 5HT1B receptor, and agonism of the 5HT1A receptor, in addition to traditional inhibition of the serotonin transporter (SERT), as shown in **Figure 1**.[7,15]
- The typical dosing schedule for vortioxetine is a starting dose of 10mg daily, with increases to 20mg daily to achieve therapeutic effect.[13]

Case

- Our patient is a 30-year-old woman with a medical history of hypertension, type 2 diabetes mellitus, and chronic kidney disease grade 4. Psychiatric history was unclear, although she did have a possible suicide attempt and subsequent psychiatric hospitalization in her teenage years.
- She presented to the emergency room with flash pulmonary edema, hypertensive emergency, and new-onset heart failure.
- Psychiatry was consulted for depressive symptoms; her initial MADRS score was 21, indicating moderate depression.[5]
- Baseline QTc was 473ms.
- Patient was started on sertraline 25mg daily; after two doses, repeat QTc was 522ms. Sertraline was discontinued.
- She subsequently developed autonomic instability, cerebrovascular accident, and hypotensive cardiac arrest requiring intubation that required stabilization in the intensive care unit.
- Following stabilization, in conjunction with the hospital electrophysiologist, a second trial of sertraline was initiated given concern for confounders of initial QTc prolongation.
- After re-initiating sertraline 25mg daily, a repeat ECG showed QTc of 533ms, and the medication was again discontinued.
- Following review of limited available safety data, a trial of vortioxetine was agreed on by both the electrophysiologist and psychiatry team. The patient was started on vortioxetine 5mg daily.
- Repeat ECG demonstrated a QTc of 481ms; subsequent ECGs continued to show QTc <500ms.
- After two weeks of treatment, her MADRS score decreased to 4, indicating remission.[5]

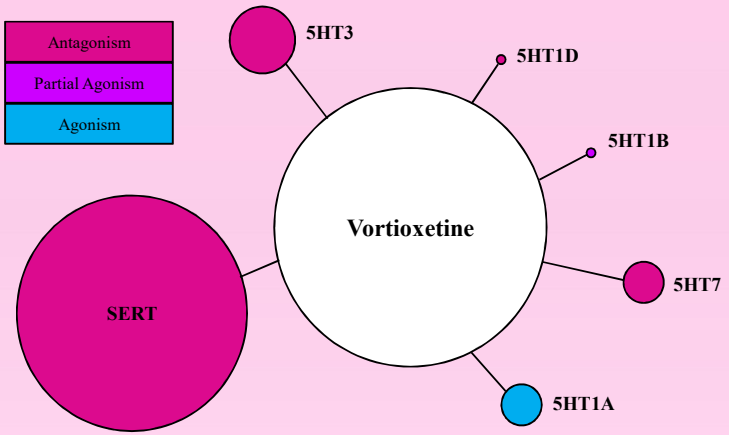

Figure 1. Receptor binding properties of vortioxetine, with relative receptor affinity indicated by size.[15]

Discussion

- Our patient had clinical remission of depressive symptoms with treatment with vortioxetine, with a decrease in MADRS score from 21 to 4, and no significant QTc prolongation.[5]
- While available studies suggest that vortioxetine does not prolong QTc, these studies were sponsored by the pharmaceutical companies manufacturing the drug.[8,9]
- Further, these studies were done only in healthy, predominantly white males,[8,9] whereas our patient had comorbidities more consistent with a geriatric patient and was a Hispanic female.
- Our patient was started at a lower-than-typical dose given concern for sensitivity to cardiac effects. Given her response to this low dose, it is possible the inward-rectifying potassium channels were insufficiently blocked to prolong QTc.[12]
- Our patient's CYP enzyme genotype was unknown; given that vortioxetine is metabolized by CYP2D6 and she responded well to a typically subtherapeutic dose, it is possible she is a CYP2D6 poor metabolizer.[14]

Conclusions

- Vortioxetine may be a cardio-safe medication in patients with complex cardiac comorbidities.
- More research is needed to investigate the safety profile of this relatively new medication in a broader range of patients, including geriatric patients, patients with a variety of medical comorbidities, women, and patients of color.

References

1. Gold SM, Köhler-Forsberg O, Moss-Morris R, et al. Comorbid depression in medical diseases. Nat Rev Dis Primers. 2020;6:69.
2. Friedrich MJ. Depression is the leading cause of disability around the world. JAMA. 2017;317:1517.
3. Cuomo A, Libri C, Barillà G, et al. QTc interval diurnal variations in patients treated with psychotropic medications: implications for the evaluation of drug induced QTc changes. Int Rev Psychiatry. 2022;34(7–8):689–692.
4. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014;75:e441–e449.
5. Müller M, Himmerich H, Kienzle B, et al. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord. 2003;77:255–260.
6. Vortioxetine [package insert]. Deerfield, IN: Takeda Pharmaceuticals America, Inc; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204447s021s022lbl.pdf. Accessed July 12, 2023.
7. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application. 5th ed. Cambridge, United Kingdom: Cambridge University Press; 2021.
8. 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. Clin Pharmacol Drug Dev. 2013;2:298–309.
9. Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol. 2016;30:242–252.
10. McClelland J, Mathys M. Evaluation of QTc prolongation and dosage effect with citalopram. Ment Health Clin. 2016;6:165–170.
11. Sicouri S, Antzelevitch C. Mechanisms underlying the actions of antidepressant and antipsychotic drugs that cause sudden cardiac arrest. Arrhythm Electrophysiol Rev. 2018;7:199–209.
12. Hsiao HT, Wang JC, Wu SN. Inhibitory effectiveness in delayed-rectifier potassium current caused by vortioxetine, known to be a novel antidepressant. Biomedicine. 2022;10:1318.
13. Stahl S. Prescriber's Guide: Stahl's Essential Psychopharmacology. 7th ed. Cambridge, United Kingdom: Cambridge University Press ed. 2020.
14. Frederiksen T, Smith RL, Wollmann BM, et al. Validation of a population pharmacokinetic model of vortioxetine using therapeutic drug monitoring data. Clin Pharmacokinet. 2021;60:1475–1486.
15. Mechanism of Action (MOA) | TRINTELLIX (Vortioxetine). https://www.trintellixhcp.com/mechanism-of-action. Accessed 11 Oct. 2023.

This case was published in *Journal of Clinical Psychopharmacology* on August 25, 2023.