

Psychotropic Drugs and Prolonged QTc Interval: Does it Really that Matter?

Sir,

Psychotropic drug-induced QTc prolongation has become increasingly a clinicians' nightmare, forcing them to refrain from prescribing very efficacious drugs, and hence, depriving patients from potential therapeutic trials.

Herein, I would emphasize some points germane to this topic in an attempt to address my rhetorical query.

QTc prolongation is feared for resultant malignant polymorphic ventricular tachycardia, what Dessertenne coined torsades de pointes (TdP).^[1]

As if ruled, acquired QTc prolongation leading to TdP is a rare clinical occurrence (cf. congenital long QT syndromes).^[2]

Second, a propensity of a certain drug to prolong QTc interval is different from its torsadogenic effect. An exemplar is amiodarone.^[3] And conversely, there are case reports of TdP in patients with apparently normal QT interval.^[4]

Third, QTc measurement is fraught with fallacies. It ideally mandates physical rest. Physiologic fluctuations^[5] are commonplace, for instance, it increases during the night, the first part of menstrual cycle, and exponentially with weight gain. Correction using Bazget's versus Fridericia's formula is primarily dependant on heart rate.^[6] Automated calculation is reliably unreliable.

Reliance on QTc prolongation as a sole surrogate marker for TdP is highly tricky and misleading. Other markers to consider include, inter alia, QTc dispersion, TPTE, flattened T-waves, postpause U-accentuation, triangulation, and monophasic action potential (MAPs).^[7]

Last but not the least, when TdP develops in the setting of QTc prolongation, the underlying mechanism is multifactorial. Mostly, it is a cumulative risk. For instance, female gender, underlying ischemic heart, polypharmacy, overdosage, dyselectrolytemia, etc.^[8]

Now, let me show how this has negatively impacted our clinical practice. In my opinion, big pharma abandoned too many promising meds in the pipeline with merely

5-ms increase in QTc above baseline!^[9] Although 60 ms increase in practice is deemed meaningful.^[10]

Second, clinicians, out of this QTc phobia, relinquished the idea of prescribing some psychotropic drugs with very attractive pharmacologic portfolios. Suffice to mention, Sertindole (Serdolect®), Ziprasidone (Zeldox®), and Citalopram (Celexa®) just to name few.

Sertindole is one of only a few metabolic-friendly atypical antipsychotics, with extrapyramidal symptoms equal to placebo, and promising procognitive actions.^[11] Unfortunately, it was withdrawn from US markets for cardiotoxicity concerns.^[12] Eckardt *et al.*^[13] refuted it. They have demonstrated that QT and MAP in case of sertindole are cycle-length independent, no effects on transmural or interventricular dispersion of repolarization, and no early after depolarization. This might be ascribed to α 1 blockade and/or I Na inhibition pharmacologic properties of sertindole.

Ziprasidone, again, a metabolic-friendly atypical antipsychotic, with MOZART study by Sacchetti *et al.* showing comparable efficacy to clozapine in resistant schizophrenia.^[14] Cardiac concerns were too refuted. Camm *et al.* revised the topic, including ZODIAC trial, and concluded modest mean increase in QTc from 4.5 to 19.5 ms in a dose-dependent fashion, with <1% QTc prolongation over 60 ms.^[15]

Citalopram is a selective serotonin reuptake inhibitor, which Lespérance *et al.* in CREATE trial found efficacious in depressed patients with coronary artery disease.^[16] Wagner *et al.*^[17] conducted a positive RCT of citalopram for major depressive disorder in children and adolescents. Nonetheless, Food and Drug Administration warned about its potential to prolong QTc at high doses and recommended a ceiling dose of 40 mg/d.^[18] Hasnain *et al.*^[19] contends that safety warnings should extent to escitalopram (Lexapro®) too. Zivin *et al.*^[20] refuted these concerns in a large cohort study finding no elevated risks of ventricular arrhythmias or all-cause, cardiac, or noncardiac mortality associated with citalopram dosages over 40 mg/d.

Quo Vadis? Clinicians should be vigilant, mindful, and cognizant of psychotropic-induced QTc prolongation, but in the absence of other risk factors and as long as

the cut-off point of 500 ms^[21] has not been reached, they should better pursue with the same medication, while keeping monitoring and not depriving patients from often-times valuable pharmacologic options for largely unsubstantiated concerns.

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