HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

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Editorial Commentary

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The real-world incidence of severe QT prolongation in patients taking antipsychotic drugs

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(Heart Rhythm 2024;21:329–330)

The increased risk of arrhythmias and sudden cardiac death (SCD) caused by drug-induced QT prolongation has been a prominent safety pharmacology concern for the last 30 years. Between 1994 and 2004, 9 drugs were either removed from the market or had their use restricted because of an unacceptably high risk of lethal ventricular arrhythmias,[1] caused by inadvertent block of *human ether-a-go-go-related gene* (hERG) potassium channels, which encode the rapid delayed-rectifier potassium current, an important contributor to cardiac repolarization.[2] The introduction of stringent preclinical testing protocols has prevented the introduction of any new drugs to the market that have an unacceptably high risk of SCD.[3] Drug-induced cardiac arrhythmias, however, remain an important clinical issue because there are drugs that increase the risk of SCD but remain on the market because they serve an important clinical need and there are no safer alternatives. Of the 41 drugs on the market in the United States that are listed as having a known risk of torsades de pointes (https://crediblemeds.org/index.php/druglist), 5 are antipsychotic drugs, the mainstay of treatment of schizophrenia and psychosis. The use of antipsychotic drugs is associated with an ~2-fold increased risk of SCD.[4] If we cannot eliminate this risk, then at the least we need to minimize the risk by identifying those patients who are at highest risk and managing them more closely.

Drug-induced torsades de pointes have a reported annual incidence in studies of hospital admissions of 4 cases per 100,000 person-years.[5] This may be an underrepresentation of the true incidence of long QT events, as out-of-hospital cases go unreported.[6–8] In a study reported in this issue of Heart*Rhythm*, Wang et al[9] ask how common drug-induced QT prolongation is in patients taking quetiapine or haloperidol, 2 commonly used antipsychotic drugs, in a real work setting. Next, they asked whether there are any biomarkers, comorbidities, or clinical features that could help identify patients at highest risk. They accessed the electronic medical records from a multicenter health care provider in Taiwan to identify all patients who received quetiapine or haloperidol therapy and had both baseline and follow-up electrocardiograms (ECGs). First, they confirmed in their cohort that there was an association between the use of quetiapine or haloperidol and the increased risk of SCD, similar to that reported previously.[4] An analysis of ECGs pre- and postcommencement of the drugs showed an increase in corrected QT (QTc) interval of +8.3 ± 51.8 ms for quetiapine users and +8.9 ± 44.0 ms for haloperidol users. This is similar to the 6–12 ms and 7–13 ms reported for terfenadine and cisapride, an antihistamine and a gastrokinetic agent, that have been withdrawn from the market.[10,11] In a comparator group of the present study, Wang et al found that a cohort of patients were taking alprazolam, a non–anti-psychotic drug without a known risk of severe QT prolongation (SQTP) and there was a +5.6 ± 35.2 ms increase in QT interval. This indicates that within this population, with an average age of ~67 years, there can be a considerable change in QT interval over time (both increase and decrease), which will have multiple contributing factors (discussed below), but there is a significant component that is likely due to a direct effect of the antipsychotic drug. Given the significant variation in QT measurements, it is notable that 13.0% of quetiapine users and 14.2% haloperidol users developed SQTP, defined as QTc interval > 500 ms or a prolongation of the QTc interval by >60 ms compared to the baseline value.

Concomitant drug use can exacerbate QT prolongation either by increasing the extent of hERG block or through more subtle drug-drug interactions.[11] The drugs producing

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https://doi.org/10.1016/j.hrthm.2023.11.012
1547-5271/$-see front matter

the greatest increase in QTc interval in quetiapine users were amiodarone (+18.2 ms increase) and dronedarone (+33.5 ms increase), which in each case increased the patient risk of developing SQTP. Furosemide likewise increased the risk of SQTP in patients taking quetiapine (+9.4 ms increase in QTc interval). Patients with SQTP were also more likely to be of advanced age (>65 years) and have hypokalemia, hypocalcemia, and/or hypomagnesemia, each known risk factors for SQTP.[12]

The most important conclusion from the study by Wang et al is that up to ~10% of patients taking quetiapine or haloperidol will develop SQTP. Thus, it would be prudent to undertake ECG before and after commencement of an antipsychotic drug. If it is an option, one could discontinue a drug causing QT prolongation and try a different antipsychotic drug. But if this is not practical, then one should pay particular attention to reducing other risk factors, such as prescription of other drugs that may exacerbate QT prolongation and be vigilant for hypokalaemia.

As with any "real-world" study, there will always be missing data that would have been nice to have. For example, there was no information on the drug doses that were used. Quetiapine and haloperidol have a dose-dependent effect on hERG block,[13,14] and it is known that SCD risk increases as dose of antipsychotic drug increases.[4] Another limitation of the study was that the age group studied was relatively old and likely included only small numbers of patients in their late teens/twenties, which is when schizophrenia is often first diagnosed and antipsychotic drug commenced. So, we cannot necessarily extrapolate the findings from the present study to this younger cohort that may have fewer comorbidities. Nevertheless, this study represents an important step forward into real-world monitoring of SQTP. It would also be valuable to explore these questions in different populations, including the UK Biobank or All of Us cohorts, where one could also look for genetic markers, for example, polygenic risk scores, that might help to identify patients most at risk of SQTP. In the meantime, the data from this study highlight the need to be vigilant for SQTP in patients taking antipsychotic drugs.

Funding Sources: Mr TeBay was supported by the Australian Government Research Training Program (RTP) scholarship.

Disclosures: The authors have no conflicts of interest to disclose.

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