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## Anti-psychotic medications and sudden cardiac arrest: more than meets the eye?

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Sudden cardiac arrest (SCA) remains an important public health problem, and is stubbornly difficult to predict or prevent. A growing literature has emerged studying psychiatric conditions, such as depression and schizophrenia, and risk of arrhythmia and SCA.<sup>1–3</sup> This field is challenging from an epidemiologic perspective, due in part to the rarity of SCA events in the general population without known heart disease, and the potential confounding factors that may influence findings.<sup>4</sup> For instance, there is increased recognition that treatments for mental illness may themselves raise cardiac risk. Antipsychotic medications are a prominent example, as they have well-known effects on the delayed rectifier potassium current, the electrocardiographic QT interval, and risk of torsades de pointes.<sup>5, 6</sup> Several prior studies have noted increased risk of SCA associated with both the typical and atypical antipsychotic medications.<sup>7–9</sup>

Now, in this issue of *HeartRhythm*, the investigators of the Oregon Sudden Unexpected Death Study group have documented novel observations relating antipsychotic medications to SCA. In this well-characterized database of SCAs that occurred from 2002 to 2009, a surprising finding was that antipsychotic use was associated with increased risk of pulseless electrical activity (PEA) compared with ventricular tachycardia/ventricular fibrillation (VT/VF). Among 818 cases of SCA, antipsychotic medication use was present among 13.6% of PEA cases, versus 4.1% of VT/VF ‘controls’. In a multivariable model that included comorbidities such as coronary disease and chronic obstructive pulmonary disease/asthma, as well as aspects about the SCA such as witnessed status and response time, the risk of PEA associated with antipsychotic use remained elevated (odds ratio 2.40, 95% CI 1.26–4.53).

It is important to consider possible alternative explanations for the results; for instance, physician prescribing behavior may contribute to confounding. Given the widespread knowledge about the risk of torsades from antipsychotic medications, physicians may avoid prescribing them to patients who might be at any perceived risk for this event. Despite the adjustment that has been performed in these analyses, there may be omitted factors, such as left ventricular systolic dysfunction, that may have prompted less frequent antipsychotic medication prescription in this group, thus resulting in underestimation of the relative association between antipsychotic medication and VT/VF compared with PEA. Also, although less likely, both torsades<sup>11</sup> and less commonly VT/VF<sup>12</sup> have been reported to

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terminate spontaneously, and may have resulted in mis-classification of some PEA cases attributed to antipsychotic use.

In interpreting these results, we must also keep in mind that underlying psychiatric illness may well be driving part of the risk of PEA. It is essentially impossible to isolate for the effects of antipsychotic medication in this type of study design. The importance of the heart/brain connection has become more widely acknowledged in recent years, and the lack of information about the presence and severity of illnesses such as schizophrenia is a limitation of the analysis.

If these findings are replicated in other studies, they present disconcerting issues for clinicians. As opposed to VT/VF, survival from out-of-hospital SCA due to PEA is significantly lower.<sup>13</sup> Further, torsades is potentially avoidable with monitoring of the QT interval in patients taking antipsychotic medications. Prior studies from the same database have identified history of syncope, Black race, female gender, and pulmonary disease as risk factors for PEA versus VT/VF.<sup>14</sup> However, there are no known electrocardiographic predictors of PEA, which makes some sense given the multiple potential causes, many of which are non-cardiac.

The authors postulate that antipsychotic medications may result in increased PEA risk by adversely impacting cardiac contractility. However, there are also data describing associations between antipsychotic medications and both pulmonary embolism<sup>15, 16</sup> and diabetic ketoacidosis,<sup>17</sup> both plausible causes of PEA. Hopefully further investigations will be able to drill down on culprit mechanisms that can potentially be modified or predicted.

In their prior review of antipsychotic medications and torsades, Drs. Glassman and Bigger concluded that psychiatrists would have to add terms like torsades de pointes, QTc interval, and potassium rectifier current to their vocabulary.<sup>5</sup> Time and further study will tell whether PEA and contractility will also need to enter their lexicon. In the meantime, disentangling the risks and benefits of anti-psychotic medications for our patients will require our best clinical judgment and close collaboration with our psychiatric colleagues.

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