

## Psychotropic Medications and the Risk of Sudden Cardiac Death

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Sudden cardiac death (SCD) accounts 1 out of 2 deaths from cardiovascular diseases.<sup>1</sup> Identification of factors increasing the risk of SCD has been a challenge for both scientists and clinicians for decades, and the risk factors of SCD have been intensively studied. Some factors have already been identified that increase the risk of SCD.<sup>2</sup> Currently recognized risk factors mainly reflect the demographic features and severity of underlying cardiac disorder itself,<sup>2,3</sup> such as male gender, abnormalities in 12-lead and 24-hour ECG, or left ventricular ejection fraction,<sup>2,3</sup> but there has been less information about the external modifiable factors, such as use of various medications, that may increase the vulnerability to fatal arrhythmias leading to SCD.

Mental disorders have been associated with increased risk of cardiovascular mortality and sudden cardiac death (SCD).<sup>4–6</sup> There is also increasing evidence suggesting that psychotropic drugs used to treat psychiatric disorders could increase the risk of SCD.<sup>7–9</sup> Despite the epidemiological evidence of an association between mental disorders and SCD, the exact pathways and pathophysiological mechanisms of these associations are not well established. Prolongation of QT interval by psychotropic drugs that block the human ether-a-go-go gene potassium channel has been proposed as one probable mechanism that may increase the vulnerability to fatal arrhythmias.<sup>10</sup>

In this journal, Wu et al have report the results of a study assessing the association of antipsychotic drugs and ventricular arrhythmias (VA) and/or SCD in a nationwide case-crossover study in Taiwan.<sup>11</sup> The authors conclude that use of antipsychotic drugs was associated with an increased risk of

combined end point of VA/SCD. Antipsychotic drugs with a high potency of the ether-a-go-go gene channel blockade had the highest risk of VA/SCD, and the risk was somewhat higher in users of first-generation versus second-generation antipsychotic drugs. The study also showed that those with a shorter duration of drug use had a higher risk of VA/SCD. The results of this large case-crossover study are in line with previous case-control and observational studies and support the concept of a proarrhythmic potential of antipsychotic drugs.

Despite the benefits of the study by Wu et al as being a large nationwide survey and assessing the role of various antipsychotic drugs separately, there are some limitations that prevent the conclusions about the potential mechanistic links between antipsychotic drugs and fatal or near-fatal arrhythmias. The end point of the study was heterogeneous by including paroxysmal ventricular tachycardia, ventricular fibrillation and flutter, cardiac arrest, instantaneous death, and sudden death in less than 24 hours from the onset of symptoms using ICD-9-CM diagnostic codes obtained from the medical records. Paroxysmal ventricular tachycardia can be sustained or nonsustained, monomorphic, or polymorphic and the mechanisms and clinical importance of these arrhythmias are different. Monomorphic nonsustained ventricular tachycardia does not carry a similar risk as polymorphic tachycardia leading to collapse or sustained ventricular tachycardia lasting several minutes. Drugs that prolong cardiac repolarization (eg, some antipsychotic drugs) are usually considered to increase risk of torsade de pointes or polymorphic ventricular tachycardia but not monomorphic tachycardia.<sup>10</sup> Arrhythmia mechanisms causing cardiac arrest, instantaneous death, and SCD are also heterogeneous. There is increasing evidence that asystole and pulseless electrical activity are even more common mechanisms than ventricular fibrillation in cases with cardiac arrest.<sup>12</sup> Even if the authors have reported separately these various end points in their Table S1, the heterogeneity of the VA/SCD to separate cases from controls may dilute the information obtained in this study.

The relative risks of VA/SCD were smaller in users versus nonusers in the study by Wu et al when compared to previous similar studies.<sup>7–9</sup> One of the reasons may be the different end point between the studies, since nonfatal VA has not

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been included as an end point of previous studies. There may also be geographic and ethnic differences in the association between psychotropic drugs and the risk of SCD. Only 22% of the patients had coronary artery disease as an underlying structural cardiac disease in the study of Wu et al from Taiwan. Ischemic heart disease is considered to be present in about 70% of the victims of SCD in Western societies, and psychotropic drugs have been strongly associated with the risk of SCD during an acute coronary event. Thus, the association between antipsychotic drugs and fatal arrhythmias may in fact be larger in white Western populations than in South-Asian populations.

Despite the data of many studies, including the current study by Wu et al, clearly showing that there is an association between antipsychotic drug use and the risk of arrhythmic death, the causal relationship is not yet completely proven. It still remains uncertain whether the mental disorder itself or antipsychotic drugs to treat them predispose to SCD. Patients with severe mental disorder can have other risk factors of cardiovascular diseases increasing the risk of SCD, such as smoking, hypertension, diabetes, obesity, or the lack of compliance with cardiovascular medications that may increase the risk of acute cardiac events leading to SCD.

Despite the lack of firm causal relationship between the use of antipsychotic drugs and SCD, it can well be recommended based on the current evidence that the QTc interval should be measured from standard 12-lead ECG after initiation of antipsychotic drugs, and that the drug and its dose should be selected individually based on this measurement. In addition, attempts should be focused on preventing coronary events in the subjects suffering from psychiatric disorders and who require antipsychotic drugs, since an acute ischemic event is the most common mode of SCD, and psychotropic drugs have been shown to increase the risk of SCD, particularly during an acute coronary event.<sup>7</sup>

## Disclosures

None.

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