Cardiac risk and schizophrenia

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Sudden cardiac death, which is defined as death from a cardiac cause within a short time (minutes to hours) after symptoms initially appear, often without warning, is a major public health problem, accounting for about 10% of all natural deaths and over 50% of all coronary mortality. Most individuals who die a sudden cardiac death have no history of heart disease.[1]

Patients with schizophrenia have been reported to be 3 times as likely to experience sudden unexpected death than individuals from the general population,[2] although the specific aspects contributing to this increased risk of death remain unclear. Different factors related to the underlying pathology, antipsychotic medications and lifestyle (e.g., smoking, general neglect of health, poor diet and decreased access to health care services) may contribute to the increased mortality in these patients. A recent study found that patients who received antipsychotic medication were 1.4 times more likely to die unexpectedly than individuals who were antipsychotic drug free.[3] However, this study did not include patients who were taking any of the atypical (second-generation) antipsychotic drugs. Cases of sudden death have been reported in subjects taking atypical antipsychotic drugs, but a recent review of these drugs indicates that they are generally safe.[4] The situation with regard to these drugs is confounded by the fact that there is an excess risk of mortality in schizophrenia even when patients are not treated with antipsychotic drugs, and a number of other medications that may be co-administered with antipsychotic drugs may also be associated with QTc prolongation,[5] as discussed below.

A number of cardiac measures shown to predict sudden cardiac death and other arrhythmias in non-diseased individuals have also been observed in patients with schizophrenia. For example, a prolonged QT interval (increased time taken for the heart to recover from the previous contraction) or QTc interval (QT interval corrected for cardiac rate) has been shown to be a risk factor for such cardiac events,[6–8] and has been observed in some individuals with schizophrenia.[9,10] Low heart rate variability (HRV), a marker of abnormal cardiac autonomic function[11] that has been shown to predict potentially fatal ventricular tachycardias in a number of disease conditions, has also been observed in patients with psychosis.[12–14] However, as most of the patients in these studies were either currently being treated with antipsychotic drugs or had previously received these medications, it is unclear whether the prolonged QT interval and the low HRV observed resulted from the antipsychotic drugs or from the disease itself.

Some, but not all, antipsychotic drugs have been shown to prolong the QTc interval, but interpretation of data is complicated by the finding that prolonged QTc intervals are often associated with high drug doses or combinations of drugs.[15,16] Patients treated with clozapine have been reported to exhibit significantly lower HRV than patients treated with olanzapine, sertindole or amisulpride.[12,17,18] Moreover, HRV has been reported to be negatively correlated with the serum levels of clozapine.[19] In a study of healthy volunteers, short-term administration of olanzapine, thioridazine and risperidone increased, decreased and had no effect, respectively, on HRV.[20]

Some antipsychotic medications have also been reported to be associated with an increased risk of diabetes and an ill-defined metabolic syndrome, sometimes referred to as syndrome X, which typically includes weight gain and abnormalities in lipid, glucose and insulin regulation.[21] Some or all of these conditions could indirectly play a role in the increased cardiac risk observed in patients with schizophrenia.[22–27] It should be noted, however, that abnormalities in glucose regulation have also been observed in medication-naïve individuals with schizophrenia.[23,28]

Autonomic dysfunction, that is, an imbalance between the sympathetic and parasympathetic systems, in schizophrenia

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may also be a "disease effect." Decreased parasympathetic activity has been reported in previously medicated, but currently unmedicated, patients with schizophrenia,[29] and autonomic deficits have been shown to be more pronounced during acute psychotic episodes in patients with first-episode schizophrenia.[30] A number of studies have suggested that the right hemisphere predominantly modulates sympathetic activity, whereas the left hemisphere predominantly modulates parasympathetic activity. Malaspina et al[31] documented relative right ear advantage on dichotic listening in patients with schizophrenia and decreased cardiac parasympathetic activity, indicating left hemisphere hyperactivation.[32] Interestingly, left hemisphere hyperactivation appeared to be more pronounced among patients with schizophrenia who had paranoid symptoms compared with those with non-paranoid symptoms,[32] suggesting that differences in parasympathetic activation may be evident between these 2 patient populations. In terms of cardiac measures, psychotic states were reported to be associated with decreased high-frequency HRV,[33,34] independent of medication treatment.[35,36]

Parasympathetic hypoactivity and sympathetic hyperactivity have also been detected in studies of depression and panic disorder,[37] and decreased parasympathetic activity has been shown in studies of alcohol dependence[38] and anorexia nervosa.[39] Stress itself can cause changes such as increased cardiac sympathetic activity and decreased parasympathetic activity, making the myocardium prone to arrhythmias, and may be responsible for some of the autonomic changes seen in these patients.[40–42] More active monitoring of cardiovascular and metabolic function will increase our knowledge of autonomic dysfunction in schizophrenia and will clarify the role, if any, of antipsychotic drugs and other medications in such dysfunction. Continued work in this area will hopefully result in the early detection of a subset of patients with schizophrenia at higher risk for cardiac abnormalities and aid the development of effective interventions to lower the risk of cardiac events in these individuals. The prospect of "tailoring" treatment interventions in those at highest risk is exciting indeed.

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JPN's Top Ten Articles, October 2005 (based on Web views on PubMed Central)

1. **Perinatal complications in children with attention-deficit hyperactivity disorder and their unaffected siblings**
   Ben Amor et al
   J Psychiatry Neurosci 2005;30(2):120-6

2. **Substance use and cognition in early psychosis**
   Pencer and Addington
   J Psychiatry Neurosci 2003;28(1):48-54

3. **Potential benefits of quetiapine in the treatment of substance dependence disorders**
   Sattar et al
   J Psychiatry Neurosci 2004;29(6):452-7

4. **Treatment of primary insomnia with melatonin: a double-blind, placebo-controlled, crossover study**
   Almeida Montes et al
   J Psychiatry Neurosci 2003;28(3):191-6

5. **Effects of diazepam on facial emotion recognition**
   Coupland et al
   J Psychiatry Neurosci 2003;28(6):452-63

6. **Amitriptyline and fluoxetine protect PC12 cells from cell death induced by hydrogen peroxide**
   Kolla et al
   J Psychiatry Neurosci 2005;30(3):196-201

7. **Lifestyle drugs, mood, behaviour and cognition**
   Young
   J Psychiatry Neurosci 2003; 8(2):87-9

8 **Adult metachromatic leukodystrophy: disorganized schizophrenia-like symptoms and postpartum depression in 2 sisters**
   Gregoric Kumperscak et al
   J Psychiatry Neurosci 2005;30(1):33-6

9. **Evidence for the activity of lamotrigine at 5-HT$_{1A}$ receptors in the mouse forced swimming test**
   Bourin et al
   J Psychiatry Neurosci 2005;30(4):275-82

10. **Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia**
    Diaz et al
    J Psychiatry Neurosci 2001;26(4):325-9