

## 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.<sup>1</sup>

Patients with schizophrenia have been reported to be 3 times as likely to experience sudden unexpected death than individuals from the general population,<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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,<sup>5</sup> 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,<sup>6-8</sup> and has been observed in some individuals with schizophrenia.<sup>9,10</sup> Low heart rate variability (HRV), a marker of abnormal cardiac autonomic function<sup>11</sup> that has been shown to predict potentially fatal ventricular tachycardias in a number of disease conditions, has also been observed in patients with psychosis.<sup>12-14</sup> 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.<sup>15,16</sup> Patients treated with clozapine have been reported to exhibit significantly lower HRV than patients treated with olanzapine, sertindole or amisulpride.<sup>12,17,18</sup> Moreover, HRV has been reported to be negatively correlated with the serum levels of clozapine.<sup>19</sup> In a study of healthy volunteers, short-term administration of olanzapine, thioridazine and risperidone increased, decreased and had no effect, respectively, on HRV.<sup>20</sup>

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.<sup>21</sup> Some or all of these conditions could indirectly play a role in the increased cardiac risk observed in patients with schizophrenia.<sup>22-27</sup> It should be noted, however, that abnormalities in glucose regulation have also been observed in medication-naïve individuals with schizophrenia.<sup>23,28</sup>

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

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Medical subject headings: antipsychotic agents; death, sudden, cardiac; schizophrenia.

*J Psychiatry Neurosci* 2005;30(6):393-5.

may also be a "disease effect." Decreased parasympathetic activity has been reported in previously medicated, but currently unmedicated, patients with schizophrenia,<sup>29</sup> and autonomic deficits have been shown to be more pronounced during acute psychotic episodes in patients with first-episode schizophrenia.<sup>30</sup> 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<sup>31</sup> documented relative right ear advantage on dichotic listening in patients with schizophrenia and decreased cardiac parasympathetic activity, indicating left hemisphere hyperactivation.<sup>32</sup> Interestingly, left hemisphere hyperactivation appeared to be more pronounced among patients with schizophrenia who had paranoid symptoms compared with those with non-paranoid symptoms,<sup>32</sup> 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,<sup>33,34</sup> independent of medication treatment.<sup>35,36</sup>

Parasympathetic hypoactivity and sympathetic hyperactivity have also been detected in studies of depression and panic disorder,<sup>37</sup> and decreased parasympathetic activity has been shown in studies of alcohol dependence<sup>38</sup> and anorexia nervosa.<sup>39</sup> 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.<sup>40-42</sup> 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.

**Competing interests:** None declared for Dr. Jindal, Ms. MacKenzie and Dr. Yeragani. Dr. Baker is a co-recipient of a Zyprexa Research Foundation grant.

**Contributors:** All the authors contributed to the conception and design of this article and its writing and gave final approval of the article for publication.

## References

- Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation* 1998;98:2334-51.
- Ruschena D, Mullen PE, Burgess P, Cordner SM, Barry-Walsh J, Drummer OH, et al. Sudden death in psychiatric patients. *Br J Psychiatry* 1998;172:331-6.
- Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001;58:1161-7.
- Capel MM, Colbridge MG, Henry JA. Overdose profiles of new antipsychotic agents. *Int J Neuropsychopharmacol* 2000;3:51-4.
- Zarate CA Jr, Patel J. Sudden cardiac death and antipsychotic drugs: Do we know enough? *Arch Gen Psychiatry* 2001;58:1168-71.
- Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978;57:1074-7.
- Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *Am Heart J* 1957;54:59-68.
- Nguyen PT, Scheinman MM, Seger J. Polymorphous ventricular tachycardia: clinical characterization, therapy, and the QT interval. *Circulation* 1986;74:340-9.
- Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo YJ, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry* 2000;61:441-6.
- Furst BA, Champion KM, Pierre JM, Wirshing DA, Wirshing WC. Possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin. *Biol Psychiatry* 2002;51:264-5.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043-65.
- Mueck-Weymann M, Rechlin T, Ehrengut F, Rauh R, Acker J, Dittmann RW, et al. Effects of olanzapine and clozapine upon pulse rate variability. *Depress Anxiety* 2002;16:93-9.
- Kim JH, Yi SH, Yoo CS, Yang SA, Yoon SC, Lee KY, et al. Heart rate dynamics and their relationship to psychotic symptom severity in clozapine-treated schizophrenic subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:371-8.
- Mujica-Parodi LR, Yeragani V, Malaspina D. Nonlinear complexity and spectral analyses of heart rate variability in medicated and unmedicated patients with schizophrenia. *Neuropsychobiology* 2005;51:10-5.
- Czekalla J, Kollack-Walker S, Beasley CM Jr. Cardiac safety parameters of olanzapine: comparison with other atypical and typical antipsychotics. *J Clin Psychiatry* 2001;62(Suppl 2):35-40.
- Stollberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. *Int Clin Psychopharmacol* 2005;20:243-51.
- Agelink MW, Majewski T, Wurthmann C, Lukas K, Ullrich H, Linka T, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. *J Clin Psychopharmacol* 2001;21:8-13.
- Eschweiler GW, Bartels M, Langle G, Wild B, Gaertner I, Nickola M. Heart-rate variability (HRV) in the ECG trace of routine EEGs: fast monitoring for the anticholinergic effects of clozapine and olanzapine? *Pharmacopsychiatry* 2002;35:96-100.
- Rechlin T, Beck G, Weis M, Kaschka WP. Correlation between plasma clozapine concentration and heart rate variability in schizophrenic patients. *Psychopharmacology (Berl)* 1998;135:338-41.
- Silke B, Campbell C, King DJ. The potential cardiotoxicity of antipsychotic drugs as assessed by heart rate variability. *J Psychopharmacol* 2002;16:355-60.
- Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol* 2004;24:e13-8.
- Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683-9.

23. Lieberman JA. Metabolic changes associated with antipsychotic use. *Prim Care Companion J Clin Psychiatry* 2004;6:8-13.
24. Chue P, Cheung R. The impact of weight gain associated with atypical antipsychotic use in schizophrenia. *Acta Neuropsych* 2004; 16:113-23.
25. McIntyre RS, Mancini DA, Pearce MM, Silverstone P, Chue P, Misener VL, et al. Mood and psychotic disorders and type 2 diabetes: a metabolic triad. *Can J Diab* 2005;29:122-32.
26. McIntyre RS, Konarski JZ. Managing overweight/obesity and diabetes mellitus in schizophrenia. *Curr Psychiatry* 2005;(Suppl):12-22.
27. Janicak P. Major mental disorders and the metabolic syndrome. *Curr Psychiatry* 2004;(Suppl):3-11.
28. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry* 2003;160:284-9.
29. Bar KJ, Letsch A, Jochum T, Wagner G, Greiner W, Sauer H. Loss of efferent vagal activity in acute schizophrenia. *J Psychiatr Res* 2005;39:519-27.
30. Dawson ME, Nuechterlein KH, Schell AM, Gitlin M, Ventura J. Autonomic abnormalities in schizophrenia. State or trait indicators? *Arch Gen Psychiatry* 1994;51:813-24.
31. Malaspina D, Bruder G, Dalack GW, Storer S, Van Kammen M, Amador X, et al. Diminished cardiac vagal tone in schizophrenia: associations to brain laterality and age of onset. *Biol Psychiatry* 1997;41:612-7.
32. Nachshon I. Hemispheric dysfunctioning in schizophrenia. *J Nerv Ment Dis* 1980;168:241-2.
33. Toichi M, Kubota Y, Murai T, Kamio Y, Sakihama M, Toriuchi T, et al. The influence of psychotic states on the autonomic nervous system in schizophrenia. *Int J Psychophysiol* 1999;31:147-54.
34. Okada T, Toichi M, Sakihama M. Influences of an anticholinergic antiparkinsonian drug, parkinsonism, and psychotic symptoms on cardiac autonomic function in schizophrenia. *J Clin Psychopharmacol* 2003;23:441-7.
35. Valkonen-Korhonen M, Tarvainen MP, Ranta-Aho P, Karjalainen PA, Partanen J, Karhu J, et al. Heart rate variability in acute psychosis. *Psychophysiology* 2003;40:716-26.
36. Malaspina D, Dalack G, Leitman D, Corcoran C, Amador XF, Yale S, et al. Low heart rate variability is not caused by typical neuroleptics in schizophrenia patients. *CNS Spectr* 2002;7:53-7.
37. Yeragani VK, Pohl R, Jampala VC, Balon R, Ramesh C, Srinivasan K. Increased QT variability in patients with panic disorder and depression. *Psychiatry Res* 2000;93:225-35.
38. Rechlin T, Orbes I, Weis M, Kaschka WP. Autonomic cardiac abnormalities in alcohol-dependent patients admitted to a psychiatric department. *Clin Auton Res* 1996;6:119-22.
39. Rechlin T, Weis M, Ott C, Bleichner F, Joraschky P. Alterations of autonomic cardiac control in anorexia nervosa. *Biol Psychiatry* 1998;43:358-63.
40. Yeragani VK, Sobolewski E, Igel G, Johnson C, Jampala VC, Kay J, et al. Decreased heart-period variability in patients with panic disorder: a study of Holter ECG records. *Psychiatry Res* 1998;78:89-99.
41. Yeragani VK, Nadella R, Hinze B, Yeragani S, Jampala VC. Non-linear measures of heart period variability: decreased measures of symbolic dynamics in patients with panic disorder. *Depress Anxiety* 2000;12:67-77.
42. Yeragani VK, Rao KA, Smitha MR, Pohl RB, Balon R, Srinivasan K. Diminished chaos of heart rate time series in patients with major depression. *Biol Psychiatry* 2002;51:733-44.

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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<sub>1A</sub> 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