The Canadian Journal of Psychiatry

Volume 60, Number 5 May 2015

Guest Editorial

Cardiac Sudden Death in Psychiatric Patients

Hiroyuki Uchida, MD, PhD[1]; Takefumi Suzuki, MD, PhD[2]

[1]Senior Lecturer, Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan; Research Scientist, Geriatric Mental Health Program, Centre for Addiction and Mental Health, Toronto, Ontario.
Correspondence: Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, JP; hiroyuki.uchida.hu@gmail.com.

[2]Senior Lecturer, Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan.

Key Words: cardiac sudden death, psychotropics, QT interval, QT prolongation, side effects

Received and accepted February 27, 2015.

It is unfortunate, but true, that mortality gaps between psychiatric patients and the general population remain considerably wide. While the data are not always consistent, it appears that life expectancy may be about 10 to 20 years shorter among patients with psychiatric conditions, compared with healthy people.[1] Previous data have identified numerous factors contributing to the shorter life expectancy, which, apart from suicide, plausibly include increased physical morbidities.[1–3] Among them, cardiac sudden death is one of the major causes of premature mortality. For example, CVDs accounted for as many as 62.8% of sudden death in 51 patients with schizophrenia in an autopsy-based study.[4] Depression was also associated with a higher hazard of 3-year mortality from heart disease, with an adjusted hazard ratio of 1.155 among 5 078 082 patients who were treated in Veterans Health Administration settings.[5] Issues in lifestyle, such as smoking, substance use, an unbalanced diet, and reduced physical activities following the onset of psychiatric illnesses may result in metabolic abnormalities, which could ultimately lead to increased risks of CVDs. In addition, various psychotropics, even newer ones, have cardiac toxicity.[6,7] Those drugs more or less prolong QT intervals by blocking potassium channel, which, in turn, can result in life-threatening ventricular arrhythmias, such as torsade de pointes although the risk differs substantially among the medications.

In light of the risk of this potentially lethal side effect, major treatment guidelines recommend routine assessment with an ECG for patients receiving drugs with such a risk,[8–10] which, however, is not always followed in clinical practice.[11] Such ignorance may be attributable, at least to some extent, to a lack of knowledge and experiences with this highly important but possibly unfamiliar issue, which is a serious concern. What does QT interval represent? What is the difference between QT interval and QTc interval? Is there any difference in QT intervals between the sexes? How about the impact of age on QT intervals? It is very likely that many of us cannot promptly and accurately answer those questions, although they are all clinically relevant.

Another concern is the potential impact of the concurrent use of 2 or more psychotropics or polypharmacotherapy on QT intervals. This is highly pertinent as recent prescription surveys have been consistent in demonstrating a prevalent use of psychotropic polypharmacy, irrespective of geographical regions.[12–16] While polypharmacy for bipolar disorders generally seems to be supported by empirical data,[17] data in favour of polypharmacy for other psychiatric conditions are still scarce and controversial at best.[18] Moreover, those previous data have mainly focused on the therapeutic effects of psychotropic polypharmacy; conversely, its negative effects have

not garnered wide attention thus far. In light of the possible pharmacokinetic and pharmacodynamic interactions of drugs concurrently prescribed, potentially increased risks of adverse consequences of combination therapy, including QT prolongation, should be prudently considered.

In the 2 In Review articles[19,20] in this issue of *The Canadian Journal of Psychiatry*, the authors have provided thorough reviews of QTc prolongation among patients with psychiatric conditions. In the first article,[19] Dr Rabkin examined the impact of age and sex on QTc intervals. Dr. Rabkin is one of the most distinguished expert cardiologists and has served on many consensus conferences for the development of the best practice guidelines for physicians. First, he shares the basic knowledge on QTc, including correction methods and its association with sudden death, with which many psychiatrists may not be familiar. Then, he reviews current evidence on the effects of age and sex as well as frequently prescribed antipsychotics and antidepressants on QTc intervals in an easy-to-understand manner. In the second article,[20] Dr Takeuchi and colleagues conducted a systematic review of the current literature on any potential association between antipsychotic polypharmacy and QTc prolongation. They conclude that the currently available evidence fails to unequivocally show that antipsychotic polypharmacy worsens QTc prolongation in general. However, in light of scarce and inconsistent evidence, clinicians are advised to remain conservative in resorting to antipsychotic polypharmacy as the combination of some QTc-prolongation liable antipsychotics has the potential to further prolong QTc interval.

Both reviews clearly emphasize potentially serious consequences of QTc prolongation and underscore the need of timely and regular ECG assessments. This is especially true for senior patients, whose QTc is already longer than their younger counterparts. Moreover, they are likely to receive a greater number of medications for psychiatric and somatic conditions; the percentage taking more than 1 medication was 70% in people aged 65 to 79 and 3% in those aged 6 to 14, according to the Canadian Health Measures Survey that was conducted from 2007 to 2011.[21] Drug-induced QTc prolongation depends on drug concentrations, which is longest at peak and shortest at trough. Given the well-described and uncharacterized risks of elevation of drug concentrations owing to interactions, polypharmacy of any sort should be avoided if at all possible unless there is a clear medical indication.

While QTc intervals should be assessed in a timely and regular manner in real-world practice, psychiatrists are advised to pay attention to other well-established somatic risk factors, such as smoking, substance use, obesity, and glucose intolerance, that are detrimental to the morbidity and mortality of cardiac diseases.[9] Such a comprehensive and holistic viewpoint, albeit with some realistic challenges, is useful to reduce CVDs and undesired outcomes among patients with serious mental illnesses.

Abbreviations

CVD	cardiovascular disease
ECG	electrocardiogram
QT	time between start of Q wave and end of T wave
QTc	corrected QT

Acknowledgements

Dr Uchida has received grants from Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, and Yoshitomi Yakuhin and speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, Abbvie, MSD, and Janssen Pharmaceutical within the past 2 years. Dr Suzuki has received speaker or manuscript fees from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Meiji Seika, Otsuka, and Weily Japan.

The Canadian Psychiatric Association proudly supports the In Review series with an honorarium to the authors.

References

1. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014;13:153–160.
2. Fazel S, Wolf A, Palm C, et al. Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders: a 38-year total population study in Sweden. Lancet Psychiatry. 2014;1:44–54.
3. Crump C, Sundquist K, Winkleby MA, et al. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry. 2013;70:931–939.
4. Ifteni P, Correll CU, Burtea V, et al. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr Res. 2014;155:72–76.
5. Zivin K, Yosef M, Miller EM, et al. Associations between depression and all-cause and cause-specific risk of death: a retrospective cohort study in the Veterans Health Administration. J Psychosom Res. 2015;78(4):324–331.
6. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014;75:e441–e449.
7. Chung AK, Chua SE. Effects on prolongation of Bazett's corrected QT interval of seven second-generation antipsychotics in the treatment of schizophrenia: a meta-analysis. J Psychopharmacol. 2011;25:646–666.
8. Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord. 2009;11:559–595.
9. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 11th ed. Chinchester (GB): John Wiley & Sons; 2012.
10. De Hert M, Cohen D, Bobes J, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry. 2011;10:138–151.
11. Ramanuj PP. Improving blood and ECG monitoring among patients prescribed regular antipsychotic medications. Ment Health Fam Med. 2013;10:29–36.
12. Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999–2004. Psychiatr Serv. 2007;58:1007–1010.
13. Nielsen J, le Quach P, Emborg C, et al. 10-year trends in the treatment and outcomes of patients with first-episode schizophrenia. Acta Psychiatr Scand. 2010;122:356–366.

14. Tsutsumi C, Uchida H, Suzuki T, et al. The evolution of antipsychotic switch and polypharmacy in natural practice—a longitudinal perspective. Schizophr Res. 2011;130:40–46.
15. Yoshio T. [The trend for megadose polypharmacy in antipsychotic pharmacotherapy: a prescription survey conducted by the psychiatric clinical pharmacy research group]. Jpn J Psychiatry Neurol. 2012;114:690–695. Japanese.
16. Xiang YT, Wang CY, Si TM, et al. Antipsychotic polypharmacy in inpatients with schizophrenia in Asia (2001–2009). Pharmacopsychiatry. 2012;45:7–12.
17. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15:1–44.
18. Fleischhacker WW, Uchida H. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol. 2014;17:1083–1093.
19. Rabkin SW. Impact of age and sex on QT prolongation in patients receiving psychotropics. Can J Psychiatry. 2015;60(5):206–214.
20. Takeuchi H, Suzuki T, Remington G, et al. Antipsychotic polypharmacy and corrected QT interval: a systematic review. Can J Psychiatry. 2015;60(5):215–222.
21. Rotermann M, Sanmartin C, Hennessy D, et al. Prescription medication use by Canadians aged 6 to 79. Health Rep. 2014;25(6):3–9.

Erratum

Hodgins S, Larm P, Ellenbogen M, et al. Teachers' ratings of childhood behaviours predict adolescent and adult crime among 3016 males and females. Can J Psychiatry. 2013;58(3):143–150.

It has come to the authors' attention that an error occurred in the results reported in their paper, which referred to "criminal charges", not "criminal convictions". All reported results were correct, but they refer to charges, not convictions.

To determine whether the associations of the teacher ratings with convictions differed from those with charges that were reported in the article, the authors recalculated the results and there are a few changes. The table below presents the odds ratios (with 95% confidence intervals) for criminal charges reported in the article and for criminal convictions based on teacher ratings of behaviour at ages 6 and 10. Odds ratios for criminal convictions that differ in significance level from those for criminal charges are marked in bold.

Table Prevalence of high HUB and high CP scores at age 6 and 10

	Violent crimes		Nonviolent crimes	
Group	Charges	Convictions	Charges	Convictions
Boys				
Age 6				
–HUB+CP	2.07 (1.03 to 4.15)	2.49 (1.23 to 5.03)	1.64 (1.00 to 2.69)	**1.48 (0.86 to 2.53)**
+HUB–CP	1.45 (0.61 to 3.45)	0.83 (0.26 to 2.75)	1.76 (1.03 to 3.00)	1.89 (1.09 to 3.30)
+HUB+CP	4.11 (2.30 to 7.34)	2.93 (1.48 to 5.79)	5.19 (3.29 to 8.18)	4.58 (2.89 to 7.26)
Age 10				
–HUB+CP	3.91 (2.17 to 7.04)	4.32 (2.31 to 8.08)	2.65 (1.67 to 4.21)	2.91 (1.80 to 4.70)
+HUB–CP	2.70 (1.16 to 6.24)	**2.37 (0.90 to 6.24**	2.03 (1.08 to 3.79)	**2.46 (1.30 to 4.68)**
+HUB+CP	2.37 (1.08 to 5.18)	2.62 (1.13 to 6.04)	2.65 (1.55 to 4.53)	3.32 (1.93 to 5.72)
Girls				
Age 6				
–HUB+CP			2.25 (0.86 to 5.88)	2.17 (0.75 to 6.28)
+HUB–CP			2.08 (0.72 to 6.02)	1.88 (0.56 to 6.29)
+HUB+CP			5.21 (2.49 to 10.93)	6.38 (3.01 to 13.54)
Age 10				
–HUB+CP			1.16 (0.27 to 4.96)	1.37 (0.32 to 5.92)
+HUB–CP			4.68 (2.14 to 10.24)	4.17 (1.75 to 9.93)
+HUB+CP			3.69 (1.48 to 9.23)	4.37 (1.73 to 11.05)

CP = conduct problems; HUB = hurtful and uncaring behaviour

The Canadian Journal of Psychiatry regrets the error and any inconvenience it may have caused.