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This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the role of the epidemiological approach to promote advances in the field of clinical psychopharmacology, with a particular attention to controversial findings. The ultimate aims are to help develop a more critical attitude towards the results of research studies published in the international literature, to promote original research projects with higher methodological standards, and to implement the most relevant results of research in every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, four key-words, one Table or Figure and up to ten references).

Corrado Barbui, *Section Editor*

Do antidepressants prolong the QT interval?

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According to a recent cross-sectional study, some antidepressants, including amitriptyline, citalopram and escitalopram, are associated with QT_c prolongation. However, the magnitude of this association is relatively small, and the clinical implications uncertain. In this article, the main strengths and weaknesses of this cross-sectional study are briefly analysed alongside recent warnings issued by regulatory authorities. Implications for research and practice are discussed.

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Cardiovascular mortality in psychiatric patients is high. Reports of sudden unexplained death in individuals exposed to psychotropic drugs have raised the possibility that part of this excess may be due to arrhythmias, as fatal arrhythmias, including torsades de pointes, may be precipitated by prolongation of ventricular repolarisation caused by some medicines (Roden, 2004). Several psychotropic drugs are associated with effects on repolarisation interval, which may lead to prolongation of rate-corrected QT interval (QT_c) on the electrocardiogram, a proxy indicator of arrhythmias and, specifically, torsades de pointes.

Although there is no clear and unambiguous evidence linking drug-induced QT_c prolongation with the risk of torsades de pointes and sudden death, drug-induced QT_c prolongation is thought to be an important marker of arrhythmias by drug regulatory authorities (Reilly *et al.* 2000). Recently, the US Food and Drug Administration (FDA) announced that the selective serotonin reuptake inhibitor citalopram and escitalopram can cause abnormal changes in the electrical activity of the heart, and issued restrictions to the use of these antidepressants in terms of therapeutic doses and in those with cardiovascular comorbidities. This warning is based on the results of a 'thorough QT/QT_c study' of citalopram and escitalopram and on some post-marketing reports of QT_c prolongation and torsade de pointes in patients taking these antidepressants (Food and Drug Administration, 2011).

The amount of available evidence has recently been expanded by a large cross-sectional study that used a pharmacovigilance approach (Castro *et al.* 2013). This study applied natural language processing and machine-learning algorithms to examine electronic health records from a large New England healthcare system encompassing more than 4 million individuals. The aim of this study was to quantify the impact of citalopram and other selective serotonin reuptake inhibitors on QT_c interval in a large and diverse clinical population.

Adult patients with at least one prescription of antidepressants or methadone between February 1990 and

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August 2011 were selected from electronic health records; a total of 38 397 adults were identified. The authors examined the proportion of subjects in different QT_c prolongation categories: QT_c values were characterised as normal (≤430 milliseconds (ms) for men, ≤450 ms for women), borderline (431–450 ms for men, 451–470 ms for women), abnormal (451–500 ms for men, 471–500 ms for women) or high (>500 ms for men and women). The association between antidepressant dose and QT_c was investigated using linear regression analyses, after adjusting for potential clinical and demographic confounding variables. For a subset of patients, change in QT_c after drug dose increase was also examined.

The study results suggested that a dose-response association with QT_c prolongation was identified for amitriptyline, citalopram and escitalopram, but not for other antidepressants. By contrast, an association with QT_c shortening was identified for bupropion. Within-subject paired observations supported the QT_c prolonging effect of citalopram (from 10 to 20 mg: mean QT_c increase 7.8 ms; from 20 to 40 mg: mean QT_c increase 10.3 ms).

The interpretation of these findings is not straightforward. A causal link between antidepressants and QT_c prolongation may be real, but it is nevertheless possible that the prolongation might be due to confounding factors. We know that many physiological and pathological factors are associated with QT changes, including age, female sex, stress, electrolytic abnormalities and cardiovascular disease. Moreover, many non-psychotropic drugs are linked to QT prolongation. It is therefore difficult to ascertain whether all possible confounding factors have been taken into consideration. A second concern is that this study failed to clarify if the relationship is specific for amitriptyline, citalopram and escitalopram or, rather, it may be generalised to all selective serotonin reuptake inhibitors or to all antidepressants. Lack of statistical power for some antidepressants leaves uncertainty on this clinically compelling issue. Another concern is that, as recognised by the study authors, the magnitude of this association is probably small, and therefore the clinical implications of a mean QT_c increase of 10 ms remains uncertain.

Recommendations for everyday clinical practice are always difficult to make (Barbui and Cipriani, 2011). However, the link between QT_c lengthening and psychotropic drugs, including antidepressants, suggests the following considerations: (a) routine monitoring may be recommended in patients continuously exposed to antidepressants and, particularly, if amitriptyline, citalopram and escitalopram are prescribed; (b) monitoring is particularly useful if other risk factors are present, including cardiovascular comorbidities and the use of other psychotropic drugs; (c) antidepressant doses should be carefully increased, as the relationship between antidepressants and QT_c seems to be dose-dependent; (d) if possible, some drug combinations, for example citalopram and haloperidol, or escitalopram and haloperidol, should be avoided, considering that the risk of QT_c lengthening might be substantially increased, as suggested by warnings issued by regulatory agencies.

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Conflict of Interest

None.

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