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 QTc 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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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 QTc prolongation categories: QTc values were characterised as normal ($\leq$430 milliseconds (ms) for men, $\leq$450 ms for women), borderline (431–450 ms for men, 451–500 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 QTc was investigated using linear regression analyses, after adjusting for potential clinical and demographic confounding variables. For a subset of patients, change in QTc after drug dose increase was also examined.

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

The interpretation of these findings is not straightforward. A causal link between antidepressants and QTc 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 QTc increase of 10 ms remains uncertain.

Recommendations for everyday clinical practice are always difficult to make (Barbui and Cipriani, 2011). However, the link between QTc 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 QTc 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 QTc lengthening might be substantially increased, as suggested by warnings issued by regulatory agencies.

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Conflict of Interest

None.

References


