

M34. ECG ALTERATIONS ASSOCIATED WITH PSYCHOTROPIC DRUG USE IN CLINICAL SETTINGS: CLINICAL AND GENETIC PREDICTORS

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Background QTc prolongation is a potentially life-threatening side effect of some antidepressants and antipsychotics, and a number of other electrocardiogram (ECG) alterations were associated with psychotropic drugs. Poor knowledge is available about the genetic risk factors of QTc prolongation during treatment with these drugs. Polymorphisms in the $\alpha 1$ -subunit of cardiac L-type calcium channel (CACNA1C) were associated with several types of arrhythmic diseases (including Long QT syndrome), but no data are available in regard to their possible effect on QTc duration during psychotropic drugs use. The present study primarily aimed to investigate QTc variation in relation to the prescription of psychotropic drugs stratified according to their cardiovascular risk [3]. The possible modulating effect of polymorphisms in the $\alpha 1$ -subunit of cardiac L-type calcium channel (CACNA1C) gene was considered. As secondary aim, we investigated other ECG alterations possibly associated with psychotropic drugs.

Methods 213 patients with a diagnosis of mood, anxiety or psychotic disorder who required a pharmacological treatment with antidepressant and/or antipsychotic drugs were included. A cross-sectional sample (n=145) had one standard ECG at baseline while a prospective sample (n=68) had a baseline and follow-up ECG. 13 SNPs in the CACNA1C gene were genotyped in both samples. An independent prospective sample was available from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. Patients having a baseline and follow-up ECG were selected (n=515) and CACNA1C polymorphisms were extracted from imputed genome-wide data. In the prospective samples changes in ECG intervals (QTc, PR, QRS, RR, and QR) between baseline and follow-up were analyzed in relation to the number of psychotropic drugs stratified according to their cardiovascular risk (from moderate-high to none). In the cross-sectional sample ECG parameters were compared among groups taking psychotropic drugs with different cardiovascular risk. The effect of genotypes on these associations was tested.

Results There was no evidence of mean QTc prolongation or increased risk of QTc prolongation ≥ 20 ms in association with risk drugs. The prescription of drugs with cardiovascular risk was less common in older subjects (p=0.04) or with cardiovascular comorbidities (p=0.02). Other factors (gender, ethnicity, baseline QTc, kidney function) affected QTc. rs1006737 modulated QTc duration/changes in the original prospective sample (p=0.04) and in cross-sectional sample (p=0.002) and four polymorphisms in linkage disequilibrium with it modulated QTc changes in the CATIE. An association between risk drugs and shorter RR interval or higher heart rate was found in all samples.

Discussion A relevant effect of psychotropic drugs with cardiovascular risk on QTc duration was not found. A number of other factors may influence QTc. CACNA1C rs1006737 may modulate the risk of QTc prolongation in patients treated with risk drugs. Finally, high resting heart rate, even within the accepted normal range, should not be overlooked in patients treated with psychotropic drugs since it was independently associated with increased risk of all-causes mortality.

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