Graduate thesis

NTNU
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Implications of psychotropic drug treatment on corrected QT interval in patients diagnosed with an eating disorder

Graduate thesis in Professional Study Medicine
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ABSTRACT

Background: Anorexia nervosa (AN) and bulimia nervosa (BN) are psychiatric disorders with potentially severe psychiatric and somatic implications. While substantial attention has been directed towards understanding the psychiatric aspects of these complex disorders, their somatic consequences, particularly in relation to cardiac health, remain a critical area of concern. In the treatment of eating disorders, psychotropic drugs, including antidepressants and antipsychotics, are commonly prescribed. However, these medications are not without potential risk, as certain classes of psychotropic drugs have been associated with QT interval prolongation (exceeding 450 ms), a condition that can predispose individuals to severe cardiac arrhythmias and sudden cardiac death.

Objective: This study aims to assess the potential risk of prolonged corrected QT interval (QTc) in patients diagnosed with anorexia nervosa or bulimia nervosa, who are treated with psychotropic drugs.

Method: We conducted a retrospective analysis of 169 patients with anorexia nervosa (n = 103), atypical anorexia nervosa (n = 28), or bulimia nervosa (n = 38), aged over 16 years, diagnosed according to ICD-10 criteria between 2002 and 2020. Psychotropic drug exposure was assessed by reviewing medical records and available serum drug concentration measurements. QT intervals were corrected using Bazett's formula, and the mean QT value was used. QTc prolongation was defined as values exceeding 450 ms. To analyze the data, we used a linear regression model, adjusting for age, diagnosis, BMI, and serum concentrations of potassium and magnesium.

Results: Among 169 patients, the mean QTc (391±34.2 standard deviations) was below the threshold for prolongation, with the lowest values observed among patients with atypical anorexia nervosa (387±30.6). 5.3% (n = 9) had prolonged QTc interval. In a linear regression analysis, QTc interval was not associated with serum concentration or defined daily dosage of olanzapine, quetiapine, citalopram, or escitalopram.

Conclusion: The findings are in alignment with prior research, suggesting that the administration of psychotropic drugs at moderate doses is not linked to clinically significant QTc interval prolongation in this patient population either.

Introduction:

Anorexia nervosa (AN) and bulimia nervosa (BN) are psychiatric disorders with potentially severe psychiatric and somatic implications. In the diagnostic systems of both the DSM and

ICD-10, anorexia nervosa and bulimia nervosa are individual diagnoses categorized by specific patterns of disordered eating (1). A central feature of anorexia nervosa is persistent weight loss, subsequently resulting in low body weight, while bulimia nervosa is characterized by episodes of binge eating followed by inappropriate compensatory behavior, such as self-induced vomiting, misuse of diuretics, or stimulant laxatives (1). The somatic consequences of eating disorders are primarily attributed to significant weight loss, malnutrition, and the aforementioned inappropriate compensatory behaviors (1). Somatic complications can affect most organs, leading to various medical issues, including cardiovascular, endocrine, gastrointestinal, respiratory, autoimmune, and urogenital complications (2).

Cardiovascular implications are of particular concern in patients with severe eating disorders. A long-term follow-up study in Denmark found an increased risk of cardiovascular events and a notably increased all-cause mortality in individuals with AN (3). The highest rise in risk was observed in those with a more severe manifestation of the eating disorder (3). Among patients with AN, reduced heart rate and bradycardia were found to be the most prevalent cardiac abnormalities (4).

The risk of prolonged corrected QT interval (QTc) measured on electrocardiograms (ECGs) are a concern associated with eating disorders. The clinical significance of a prolonged QTc lies in its association with a heightened risk of severe cardiac arrhythmias, including life-threatening ventricular arrhythmias such as torsade de pointes and sudden cardiac death (4). The risk of QTc interval prolongation is notably elevated in individuals with eating disorders, primarily due to a confluence of factors. Among these factors is the common occurrence of electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, in patients with AN or BN (5,1). These electrolyte imbalances directly influence cardiac electrical activity and can lead to QTc prolongation, increasing the risk of arrhythmias (5).

The use of psychotropic medications, such as antidepressants and antipsychotics in the treatment of eating disorders, can impact the risk of prolonged QTc in this patient population (1). Some of these medications have been associated with QT interval prolongation (6,7). Additionally, emotional factors such as anxiety can impact cardiac functions and raise the risk of QT prolongation (8).

In Norway, antidepressants are generally not indicated for AN due to their limited efficacy (12). However, they are prescribed for AN patients with comorbid major depression, as in the case of other patients (13). Notably, in Norway, fluoxetine is the sole antidepressant approved for the treatment of BN (1) (24,25). Among selective serotonin reuptake inhibitors (SSRIs), citalopram and escitalopram are the only ones that are associated with an increased risk of prolonged QT interval, unless there is a predetermined vulnerability (6,7,16).

Administration of antipsychotic medications can increase the likelihood of experiencing ventricular arrhythmia and/or sudden cardiac death (17). Studies show that olanzapine may carry a slightly higher risk, while quetiapine appears to have no significant associations with the risk of developing arrhythmias (17). Performing an ECG before initiating antipsychotic treatment can be helpful, especially when combining medications that can cause prolonged QTc (18).

Despite the aforementioned risk factors, research findings regarding the association between prolonged QTc and eating disorders vary, with some studies identifying significant QTc prolongation (10), while others fail to identify such an association (9) (11). This disparity underscores the need for further exploration into the relationship between prolonged QTc and AN or BN, particularly considering the potential cardiac risks entailed by these disorders and their treatment.

By studying the risk of prolonged QT interval in patients with AN or BN, we can elucidate potential cardiac complications associated with severe eating disorders and the applied psychopharmacological treatment, ultimately improving patient safety and care. Psychotropic drugs, including antipsychotics and SSRIs, are commonly prescribed as adjunctive treatments for patients with AN or BN (19). However, there is evidence suggesting that certain psychotropic drugs may be associated with QT interval prolongation, posing an additional risk to patients already vulnerable to cardiac complications (10,17,18). A better understanding of the specific risks associated with psychotropic drugs and QT interval prolongation in the context of AN and BN is crucial for clinicians when making treatment decisions to minimize potential adverse cardiac events.

Methods

Design and subjects

This retrospective observational study included patients admitted to outpatient and inpatient treatment at the Regional Center for Eating Disorder (Regionalt Kompetansesenter for Spiseforstyrrelser, RKSF), Levanger, Norway, between 2002 and 2020. The inclusion criteria for the study were patients aged sixteen or older with a confirmed diagnosis of F50.0 anorexia nervosa, F50.1 atypical anorexia nervosa, F50.2 bulimia nervosa, or F50.3 atypical bulimia according to ICD-10 (20). Patients were required to have an available ECG. Out of 1025 adolescents assessed, 169 met the inclusion criteria and were enrolled in the study. We examined the antipsychotic drugs olanzapine and quetiapine and the SSRIs citalopram and escitalopram intake by using the daily dose and serum concentration of the drug as exposure variables.

Data collection

The data for this study were collected from a registry at RKSF, Levanger, Norway, which has been utilized for previous follow-up studies (21). Patients have provided verbal or written consent and have the option to withdraw from the registry at any time. Exposure to psychotropic drugs was investigated and mapped by reviewing medical records (curve sheets and summary core records) and available measurements of serum drug concentrations performed at St. Olav´s University Hospital, Trondheim, Norway. Dosage levels for each specific drug were derived based on serum concentration measurements at the time of assessment. In cases where serum concentrations were not measured, the dosage was obtained from the moment the ECG was recorded.

Assessment of prolonged QT intervals

All inpatients at RKSF typically undergo a 12-lead ECG examination assessing QTc interval and other potential abnormalities at admission or during their stay. The registered ECG included in the study was reviewed by a cardiologist blinded to the drug exposure variables. Measurements were conducted using the tangent method, and both the QT interval and RR interval were rounded to the nearest 10 milliseconds. Bazett's formula was applied to calculate the corrected QT interval (QTc). QTc=QT interval (in milliseconds) divided by the square root of the RR interval (in seconds). QT intervals were measured with a caliper in leads II and V_5, and the longest of these intervals was used in the subsequent analysis. Three

consecutive complexes were measured in regions where the RR interval exhibited the highest regularity, and the resulting average of these measurements was utilized. For frequency correction, the previous RR interval was employed, except in cases where there where an insufficient number of complexes were available; in such instances, the following RR interval was used. In cases involving arrhythmia or bradycardia, a limited number of complexes were available for measurements. In some ECGs, only average measurements were accessible as the complete ECG was not stored. Consequently, only a single QT interval was available for each lead, and the frequency measurement was determined using the machine's frequency measurement. Prolongation of QTc is defined as QTc values above 450 ms.

Analysis

We employed linear regression using QTc as a continuous outcome variable. Psychotropic drugs including olanzapine, quetiapine, citalopram, and escitalopram, were included as covariates, one at a time. We treated defined daily dosages and serum concentrations as continuous variables. For individuals not using the drug, both the dosage and concentration were set to zero.

In our analysis, we included the following drugs as covariates, examining them individually: olanzapine and quetiapine, as well as the SSRIs citalopram and escitalopram. Initially, we performed adjustments for potential confounders, starting with age and diagnosis (including AN, atypical AN, and BN). Subsequently, we further adjusted for additional variables, namely serum potassium concentrations, serum magnesium concentrations, and BMI. This study allowed for the consideration of serum concentrations of the psychotropic drugs taken up to 4 months before or after the ECG measurement.

In this study, we chose to exclude patients with a BMI > 30 kg/m^2, as this threshold corresponds to obesity, a condition that may inherently increase the risk of prolonged QT interval (22). Consequently, we had only one participant remaining in the F50.3 atypical BN category; this participant was grouped with those having F50.2 BN. Additionally, due to the limited number of male patients, they were excluded from the analysis (Table 2). This subgroup comprised six participants, all of whom were diagnosed with F50.0 AN.

Ethical considerations

The study is approved by the Regional Committee for Medical and Health Research Ethics (REK) in Central Norway and the Data Access Committee in Nord-Trøndelag Hospital Trust.

Variables

We expressed the daily dose for each subject as the number of defined daily doses (DDD) taken (10 mg escitalopram and olanzapine; 20 mg citalopram; 400 mg quetiapine) (23). The analyses of the serum concentrations were performed at the Department of Clinical Pharmacology, St. Olavs University Hospital, using previously published analytical methods (24,25). The concentrations of the various drugs were related to the reference interval of the respective drug (26) and expressed as the measured concentration of the drug divided by the middle value of the reference interval for the same drug: citalopram 140 ng/mL (70-350 ng/mL), escitalopram 45 ng/mL (25-115 ng/mL), olanzapine 20 ng/mL (10-50 ng/mL), and quetiapine 350 ng/mL (100-800 ng/mL).

Results

Of the 169 patients included, 62 used psychotropic drugs; 16 were prescribed olanzapine, 11 quetiapine, 21 citalopram, and 12 escitalopram (Table 1). The mean QTc was 391 ms (386-396, 95% confidence interval). In most cases, the QTc values remained below the threshold for QTc prolongation of 450 ms, with the exception of nine patients, all with the diagnosis of AN (Table 3).

Table 1. Sample characteristics at inclusion. Depending on the type of variable, data is displayed either as mean values accompanied by standard deviations or as numerical figures along with corresponding percentages in parentheses.

	Total (N) 169	**Anorexia nervosa (N)** 103 (60.9%)	**Atypical anorexia nervosa (N)** 28 (16.6%)	**Bulimia Nervosa (N)** 38 (22.5%)
Age (years), mean±SD	22.6±7.0	22.3±6.9	23.1±8.3	23.0±6.4
BMI (kg/m^2), mean±SD	17.3±3.2	15.5±1.9	19.4±2.6	20.6±2.5
Serum potassium (mmol/L), mean±SD	3.72±0.79	3.67±0.89	3.74±0.80	3.84±0.41
Serum magnesium (mmol/L), mean±SD	0.67±0.38	0.67±0.38	0.63±0.38	0.68±0.38
Time from serum to ECG (months), mean±SD	0.36±0.90	0.38±0.93	0.25±0.64	0.40±1.00
QTc (s), mean±SD	391±34.2	393±37.7	387±30.6	390±26.0
Olanzapine prescribed, N (%)	18 (11%)	14 (14%)	2 (7%)	2 (5%)

Olanzapine DDD, mean±SD	N=16 0.73±0.45	N=12 0.75±0.51	N=2 0.63±0.18	N=2 0.75±0.35
Olanzapine relative serum concentration (mmol/L), mean±SD	N=11 0.67±0.20	N=8 0.63±0.21	_ _ _ _ _	N=3 0.80 ± 0.14
Quetiapine prescribed, N (%)	11 (7%)	5 (5%)	2 (7%)	4 (11%)
Quetiapine DDD, mean±SD	N=11 0.27±0.23	N=5 0.23±0.20	N*=2 0.47±0.40	N=4 0.23±0.19
Quetiapine relative serum concentration, N (%)	N=1 0.25	_ _ _ _ _	0.25	_ _ _ _ _
Citalopram prescribed, N (%)	21 (12%)	12 (12%)	5 (18%)	4 (11%)
Citalopram DDD, mean±SD	N=21 2.1±0.68	N=12 2.0±0.80	N=5 2.1±0.42	N=4 2.25±0.65
Citalopram relative serum concentration (mmol/L), mean±SD	N=17 1.82±1.17	N=10 1.94±1.42	N=4 2.01±0.43	N=3 1.19±0.92
Escitalopram prescribed, N (%)	12 (7%)	8 (8%)	2 (7%)	2 (5%)
Escitalopram DDD, mean±SD	N=13 1.58±0.70	N=8 1.31±0.59	N=2 2.00±0.00	2.00±1.00
Escitalopram relative serum concentration (mmol/L), mean±SD	N=5 1.12±0.80	N=2 1.34±1.40	N=1 0.80± 0.0	N=2 1.05±0.64

BMI: body mass index.
SD: standard devation.
DDD: defined daily dosage.
QTc: QT interval corrected using Bazett's formula.

Table 2. Excluded patients from the analyses.

QTc (ms)	Diagnosis	Sex	BMI (kg/m^2)	Medication
357	AN	Male	14.0	No prescribed medications.
381	AN	Male	11.7	No prescribed medications.
341	AN	Male	15.0	Prescribed both escitalopram (DDD of 2.00), and olanzapine (DDD of 0.25). No serum concentration was measured.
368	AN	Male	13.8	Prescribed both citalopram (DDD of 5.00) and olanzapine (DDD of 0.50), with a relative serum concentration of 2.31 for citalopram and 0.15 for olanzapine.
388	AN	Male	12.4	No prescribed medications.
370	AN	Male	14.0	No prescribed medications.

Table 3. Patients with a QTc interval exceeding 450 ms.

QTc interval	**Diagnosis**	**Medication**	**Note**
573 ms	AN	Prescribed fluoxetine (DDD of 3.0).	To ensure the accuracy of this outlier, a second cardiologist was consulted. Their evaluation confirmed the validity of this measurement.
500 ms	AN	Not prescribed medications	Sinus arrhythmia.
489 ms	AN	Prescribed both olanzapine (DDD of 0.25) and citalopram (DDD 0.5), with a relative serum concentration of 0.18 for citalopram and 0.32 for olanzapine.	Only one QT measurement was available, and serum concentration was measured 1.8 months after the ECG.

471 ms	AN	No prescribed medications.	Uncertain measurements.
458 ms	AN	Prescribed quetiapine (DDD of 0.13), no serum concentration was measured.	
456 ms	AN	No prescribed medications.	
454 ms	AN	No prescribed medications.	
2 x 450 ms	AN	No prescribed medications.	

The mean BMI overall was 17.3 kg/m^2, ranging from 8.7 kg/m^2 to 25.1 kg/m^2. Only one participant did not have a registered weight. This participant was diagnosed with F50.0, and a clinical assessment has been made where the participant in question was clinically underweight and had a BMI <17.5 according to ICD-10 (20). The distribution was a mean BMI of 15.5 kg/m^2 for AN, a mean of 19.4 kg/m^2 for atypical AN, and 20.6 kg/m^2 for BN.

For those with measured serum concentrations, the dose of the medication is registered at the given time of the sample taken. The mean relative serum concentration for each drug was 0.67 mmol/L for olanzapine, 0.27 mmol/L for quetiapine, 1.82 mmol/L for citalopram, and 1.12 mmol/L for escitalopram. The mean DDD for each of the drugs was 0.73 for olanzapine, 0.27 for quetiapine, 2.07 for citalopram, and 1.58 for escitalopram (23).

2.96% (N=5) patients did not have any labs available in their records, either due to samples not being taken or being taken by their general practitioner. 26.04% (N=44) of the patients with available measurements were below the reference interval (RI) for serum potassium (3.6 mmol/L), and only 0.60% (N = 1) had values above the RI (6.0 mmol/L) (27). 1.18% (N=2) of patients had lower values than the RI of serum magnesium, and 15.38% (N=26) had values over the RI for serum magnesium (0.71-0.94 mmol/L) (28). 23.08% (N=39) of the patients did not have their blood tested or had no measured magnesium.

Results from the linear regression model are summarized in Table 4, both unadjusted and adjusted for age and diagnosis. For results adjusted for all potential confounders, please refer to Table 5 in the attached materials.

Table 4. We conducted linear regression analyses to assess the impact of the psychotropic drugs, including olanzapine, quetiapine, citalopram, and escitalopram, on QTc interval. Covariates considered in the analysis included both defined daily dosage (DDD) and relative serum concentration. Below are the regression coefficients (B), with values presented for unadjusted and adjusted models, along with corresponding 95% confidence intervals (CIs) and p-values.

Drug	Covariate	Adjustment	*B*	95% CI	*P-value*
Quetiapine	Defined daily dose	Unadjusted values	-15.0	-99.4 to 69.4	0.70
		Adjusted values	19.4	-127.9 to 89.2	0.68
Olanzapine	Defined daily dose	Unadjusted values	1.1	-40.0 to 42.1	0.96
		Adjusted values	-1.9	-51.3 to 47.5	0.93
	Relative serum	Unadjusted	-61.1	-195.6 to 73.4	0.32
		Adjusted values	-60.0	-174.8 to 54.8	0.24
Citalopram	Defined daily dose	Unadjusted values	**-32.5**	**-50.0 to -15.0**	**<0.001**
		Adjusted values	**-30.3**	**-47.7 to -12.9**	**0.002**
		Adjusted for all	**-36.9**	**-58.9 to -14.8**	**0.003**
	Relative serum concentration	Unadjusted values	-10.0	-25.8 to 5.8	0.20
		Adjusted values	-7.1	-24.5 to 10.2	0.39
Escitalopram	Defined daily dose	Unadjusted values	11.3	-8.7 to 31.4	0.24
		Adjusted values	13.7	-13.6 to 41.1	0.28
	Relative serum concentration	Unadjusted values	11.2	-11.2 to 33.6	0.21
		Adjusted values	-2.2	-2.2 to -2.2)	- - - -

Adjusted values: adjusted for age and diagnosis.
Adjusted for all: adjusted for BMI, serum potassium, and serum magnesium.

Discussion

Our study aimed to investigate the potential correlation between the psychotropic drugs olanzapine, quetiapine, citalopram, and escitalopram and prolonged QTc interval. The primary outcome of our study did not reveal any significant associations between the drugs, their doses, relative serum concentrations, and QTc interval prolongation.

The lack of statistically significant associations between quetiapine, olanzapine, and escitalopram, and QTc interval prolongations can likely be attributed to the relatively modest doses administered, with a mean defined daily dose (DDD) of 0.73 for olanzapine, 0.27 for quetiapine, and 1.58 for escitalopram. This suggests that within the range of doses studied, these medications do not substantially impact QTc intervals in our patient population.

However, a notable finding in our study was the significant negative association between the defined daily dose of citalopram (mean DDD of 2.01) and the QTc interval ($p<0.001$). This significant associations remained consistent even after adjustments for various factors ($p=0.002$ and $p=0.003$).

This unexpected result raises questions about the relationship between citalopram and QTc interval regulation. While our study found that higher defined daily doses of citalopram were associated with a reduction in the QTc interval in the studied population, it is essential to

interpret this finding cautiously. Further investigation is warranted to understand the mechanisms underlaying this association and to determine whether it has clinical implications.

The study, while acknowledging its limited sample size, aims to maximize the utility of the available data. Despite the constraints imposed by a smaller sample size, our study provides insights into the safety of the use of psychotropic drugs in a vulnerable patient group. The patients were included from a regional center, which indicated a greater severity of their eating disorders. Although our study may not have the extensive size of a larger investigation, these patients are representative of the patient group.

Furthermore, our study covers a wide spectrum of the disorder across different age groups, including patients ranging from 16 to 60 years old. This diversity enables us to explore variations in disorder characteristics, treatment responses, and outcomes among different age cohorts. To ensure standardized and consistent classifications of patients' diagnoses, the study employs international diagnostic criteria (ICD-10). This standardization allows for better comparability across various studies, populations, and healthcare settings. The blood tests employed in the study offer reliable and objective evaluations. Additionally, we employed blinded QTc measurements conducted by a cardiologist. This rigorous approach enhances the reliability and accuracy of our cardiac assessments.

While the use of ICD-10 ensures standardization, it is essential to recognize that diagnostic categories within the system can encompass a range of presentations and severity levels, potentially affecting the accuracy and specificity of our findings. The study specifically focuses on the risk of prolonged QTc among patients with AN or BN treated with psychotropic drugs. As this targeted approach allows for focused analysis, it limits the generalizability of the finding to other populations or conditions.

The study design entails a weakness as cross-sectional studies can reveal associations between variables but are limited in establishing causal relationships due to their inability to assess temporal or causal sequences.

Additionally, the missing serum concentrations for olanzapine (n=7), quetiapine (n=10, citalopram (n=4), and escitalopram (n=7) represent a limitation. The missing data can impact the results in a way that our model may not fully reflect the real-world scenario.

The time gap between serum concentration sampling and ECG measurements was set at four months, providing us with a dataset of 34 serum concentrations for analysis. Over this period, various factors, including the severity of the eating disorder and electrolyte imbalances, could potentially to undergo substantial changes. Most serum samples were collected within a twoweek window before or after the ECG measurement, supporting a reasonable assumption that the medications were prescribed near the ECG assessment.

Given the factors mentioned, future studies should prioritize increasing the sample size to further enhance statistical power. This expansion will allow for more robust analyses, enabling the detection of smaller yet clinically significant effects. Such efforts can contribute to a more comprehensive understanding of the relationship between eating disorders, psychotropic drug use, and QTc prolongation, ultimately advancing the care and treatment of individuals affected by these conditions.

In conclusion, our study did not find a significant relationship between psychotropic drugs, including quetiapine, olanzapine, and escitalopram, and QTc prolongation. These findings suggests that the doses and serum concentrations of these drugs within the range studied are unlikely to have a clinically significant impact on QTc prolongation. However, the significant negative association between higher citalopram doses and QTc intervals warrants further exploration to clarify its clinical relevance and to guide safe prescribing practices.

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Tables for the study: Implications of psychotropic drug treatment on corrected QT interval in patients diagnosed with an eating disorder.

Table 1. Sample characteristics at inclusion. Depending on the type of variable, data is displayed either as mean values accompanied by standard deviations or as numerical figures along with corresponding percentages in parentheses.

	Total (N) 169	**Anorexia nervosa (N)** 103 (60.9%)	**Atypical anorexia nervosa (N)** 28 (16.6%)	**Bulimia Nervosa (N)** 38 (22.5%)
Age (years), mean±SD	22.6±7.0	22.3±6.9	23.1±8.3	23.0±6.4
BMI (kg/m^2), mean±SD	17.3±3.2	15.5±1.9	19.4±2.6	20.6±2.5
Serum potassium (mmol/L), mean±SD	3.72±0.79	3.67±0.89	3.74±0.80	3.84±0.41
Serum magnesium (mmol/L), mean±SD	0.67±0.38	0.67±0.38	0.63±0.38	0.68±0.38
Time from serum to ECG (months), mean±SD	0.36±0.90	0.38±0.93	0.25±0.64	0.40±1.00
QTc (s), mean±SD	391±34.2	393±37.7	387±30.6	390±26.0
Olanzapine prescribed, N (%)	18 (11%)	14 (14%)	2 (7%)	2 (5%)
Olanzapine DDD, mean±SD	N=16 0.73±0.45	N=12 0.75±0.51	N=2 0.63±0.18	N=2 0.75±0.35
Olanzapine relative serum concentration (mmol/L), mean±SD	N=11 0.67±0.20	N=8 0.63±0.21	_ _ _ _ _	N=3 0.80 ± 0.14
Quetiapine prescribed, N (%)	11 (7%)	5 (5%)	2 (7%)	4 (11%)
Quetiapine DDD, mean±SD	N=11 0.27±0.23	N=5 0.23±0.20	N*=2 0.47±0.40	N=4 0.23±0.19
Quetiapine relative serum concentration, N (%)	N=1 0.25	_ _ _ _ _	0.25	_ _ _ _ _
Citalopram prescribed, N (%)	21 (12%)	12 (12%)	5 (18%)	4 (11%)
Citalopram DDD, mean±SD	N=21 2.1±0.68	N=12 2.0±0.80	N=5 2.1±0.42	N=4 2.25±0.65
Citalopram relative serum concentration (mmol/L), mean±SD	N=17 1.82±1.17	N=10 1.94±1.42	N=4 2.01±0.43	N=3 1.19±0.92
Escitalopram prescribed, N (%)	12 (7%)	8 (8%)	2 (7%)	2 (5%)
Escitalopram DDD, mean±SD	N=13 1.58±0.70	N=8 1.31±0.59	N=2 2.00±0.00	2.00±1.00
Escitalopram relative serum concentration (mmol/L), mean±SD	N=5 1.12±0.80	N=2 1.34±1.40	N=1 0.80± 0.0	N=2 1.05±0.64

BMI: Body mass index.
DDD: Defined daily dosage.
QTc: QT interval corrected using Bazett's formula.

Table 2. Excluded patients from the analyses.

QTc (ms)	Diagnosis	Sex	BMI (kg/m^2)	Medication
357	AN	Male	14.0	No prescribed medications.
381	AN	Male	11.7	No prescribed medications.

341	AN	Male	15.0	Prescribed both escitalopram (DDD of 2.00), and olanzapine (DDD of 0.25). No serum concentration was measured.
368	AN	Male	13.8	Prescribed both citalopram (DDD of 5.00) and olanzapine (DDD of 0.50), with a relative serum concentration of 2.31 for citalopram and 0.15 for olanzapine.
388	AN	Male	12.4	No prescribed medications.
370	AN	Male	14.0	No prescribed medications.

Table 3. Patients with a QTc interval exceeding 450 ms.

QTc interval	**Diagnosis**	**Medication**	**Note**
573 ms	AN	Prescribed fluoxetine (DDD of 3.0).	To ensure the accuracy of this outlier, a second cardiologist was consulted. Their evaluation confirmed the validity of this measurement.
500 ms	AN	Not prescribed medications	Sinus arrhythmia.
489 ms	AN	Prescribed both olanzapine (2.5 mg, DDD 0.25) and citalopram (10 mg, DDD 0.5), with relative serum concentration of 0.18 for citalopram and 0.32 for olanzapine.	Only one QT measurement available, and serum concentration was measured 1.8 months after the ECG.
471 ms	AN	No prescribed medications.	Uncertain measurements.
456 ms	AN	No prescribed medications.	
454 ms	AN	No prescribed medications.	
2 x 450 ms	AN	No prescribed medications.	

Table 4. We conducted linear regression analyses to assess the impact of the psychotropic drugs, including olanzapine, quetiapine, citalopram, and escitalopram, on QTc interval. Covariates considered in the analysis included both defined daily dosage (DDD) and relative serum concentration. Below are the regression coefficients (B), with values presented for unadjusted and adjusted models, along with corresponding 95% confidence intervals (CIs) and p-values.

Drug	Covariate	Adjustment	*B*	95% CI	*P-value*
Quetiapine	Defined daily dose	Unadjusted values	-15.0	-99.4 to 69.4	0.70
		Adjusted values	19.4	-127.9 to 89.2	0.68
Olanzapine	Defined daily dose	Unadjusted values	1.1	-40.0 to 42.1	0.96
		Adjusted values	-1.9	-51.3 to 47.5	0.93
	Relative serum	Unadjusted	-61.1	-195.6 to 73.4	0.32
		Adjusted values	-60.0	-174.8 to 54.8	0.24
Citalopram	Defined daily dose	Unadjusted values	**-32.5**	**-50.0 to -15.0**	**<0.001**
		Adjusted values	**-30.3**	**-47.7 to -12.9**	**0.002**
		Adjusted for all	**-36.9**	**-58.9 to -14.8**	**0.003**
	Relative serum concentration	Unadjusted values	-10.0	-25.8 to 5.8	0.20
		Adjusted values	-7.1	-24.5 to 10.2	0.39
Escitalopram	Defined daily dose	Unadjusted values	11.3	-8.7 to 31.4	0.24
		Adjusted values	13.7	-13.6 to 41.1	0.28

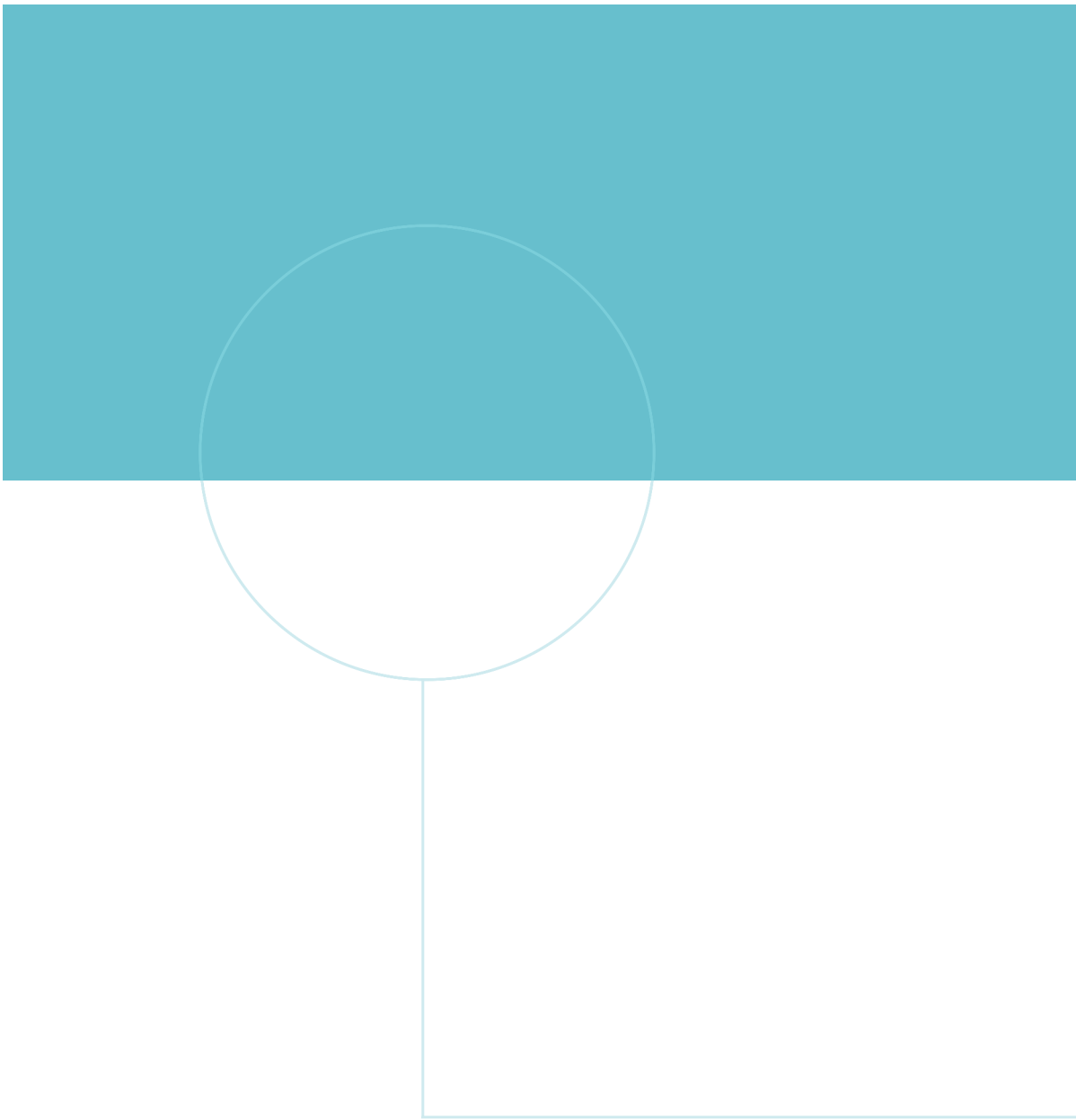
	Relative serum concentration	Unadjusted values	11.2	-11.2 to 33.6	0.21
		Adjusted values	-2.2	-2.2 to -2.2)	- - - -

Adjusted values: adjusted for age and diagnosis.
Adjusted for all: adjusted for BMI, serum potassium, and serum magnesium.

Table 5. We conducted linear regression analyses to assess the impact of the psychotropic drugs, including olanzapine, quetiapine, citalopram, and escitalopram, on QTc interval. Covariates considered in the analysis included both defined daily dosage (DDD) and relative serum concentration. Below are the regression coefficients (B), with values presented for unadjusted and adjusted models, along with corresponding 95% confidence intervals (CIs) and p-values.

Drug	Covariate	Adjustment	*B*	95% CI	*P-value*
Quetiapine	Defined daily dosage	Unadjusted values	-15.0	-99.4 to 69.4	0.70
		Adjusted values	19.4	-127.9 to 89.2	0.68
		Adjusted for all	-45.2	-247.5 to 157.2	0.53
Olanzapine	Defined daily dose	Unadjusted values	1.1	-40.0 to 42.1	0.96
		Adjusted values	-1.9	-51.3 to 47.5	0.93
		Adjusted for all	-11.7	-64.2 to 40.9	0.62
	Relative serum concentration	Unadjusted	-61.1	-195.6 to 73.4	0.32
		Adjusted values	-60.0	-174.8 to 54.8	0.24
		Adjusted for all	-166.9	-523.5 to 189.6	0.18
Citalopram	Defined daily dose	Unadjusted values	-32.5	-50.0 to 15.0	< 0.001
		Adjusted values	-30.3	-47.7 to -12.9	0.002
		Adjusted for all	-36.9	-58.9 to -14.8	0.003
	Relative serum concentration	Unadjusted values	-10.0	-25.8 to 5.8	0.20
		Adjusted values	-7.1	-24.5 to 10.2	0.39
		Adjusted for all	-7.0	-28.5 to 14.5	0.48
Escitalopram	Defined daily dose	Unadjusted	11.3	-8.7 to 31.4	0.24
		Adjusted values	13.7	-13.6 to 41.1	0.28
		Adjusted for all	15.6	-18.8 to 49.1	0.29
	Relative serum concentration	Unadjusted	11.2	-11.2 to 33.6	0.21
		Adjusted values	-2.2	-2.2 to -2.2)	- - - - -

Adjusted values: adjusted for age and diagnosis.
Adjusted for all: adjusted for BMI, serum potassium, and serum magnesium.



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