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# Monitoring of QTc in subjects hospitalized for 1 year in an acute psychiatric ward treated with clotiapine and other associated antipsychotics: a retrospective study

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***Abstract***

**Background:** Many antipsychotic medications are responsible for prolonging QTc, a risk factor for sudden death, which is one of the main causes of reduced life expectancy in patients with mental health disorders.

**Objectives:** To evaluate the cardiac safety profile of clotiapine in a naturalistic setting.

**Design:** This observational, retrospective study included 70 subjects hospitalized at the Service of Psychiatry Diagnosis and Care in Modena from February 1, 2023 to July 31, 2024, treated with clotiapine.

**Methods:** Demographic and clinical data were collected, along with electrocardiographic measurements (QTc) taken at the start of treatment (T0), after at least 7 days of therapy (T1), and at further follow-up (T2) after 7–21 days. Prolongation was considered when QTc exceeded 500 ms or an increase of 60 ms compared to baseline, according to international standards.

**Results:** QTc prolongation was limited ($m = 4.59$ ms), representing an increase of 1.07%, without reaching thresholds of significant clinical risk. Subjects with an increase equal to or greater than the median ($M = 3.5$) of QTc increase at T1 accounted for half of the sample, and only one patient had an increase greater than 60 ms.

**Conclusion:** Clotiapine treatment, also in combination with haloperidol, had minimal prolongation of QTc within the limits of clinical safety. A stabilization of QTc over time was observed, indicating a possible adaptation to treatment. Methodological limitations of this study call for further research.

## Plain language summary

### Monitoring clotiapine safety in subjects hospitalized over one year in an acute psychiatric ward

Many antipsychotic drugs are responsible for sudden death, which is a major cause of reduced life expectancy in patients with mental health disorders. In a naturalistic setting of an acute psychiatric ward, we evaluate the cardiac safety profile of clotiapine, an antipsychotic drug often used for the management of agitated behavior. We analyzed an ECG parameter (QTc) that may be responsible for arrhythmia and sudden death. We found that this drug, even in combination with haloperidol, had minimal QTc prolongation within the limits of clinical safety.

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## Introduction

In individuals with schizophrenia, cardiovascular diseases are responsible for nearly 50% of deaths and a reduction in life expectancy, and the incidence of sudden cardiac death (SCD) is about four times higher than in the general population. While most SCDs are due to ischemic heart disease, which is recognized as a specific risk factor, about 10% of SCDs are unexplained and are thought to be caused by cardiac arrhythmias.[1]

A Japanese study evaluated parasympathetic activity in 53 Japanese patients with schizophrenia suggesting that parasympathetic dysfunction leads to a sympathetic predominance which could influence the severity of schizophrenia[2] and represent a risk factor for SCD.[3] Whole-genome studies in schizophrenic subjects suggested evidence of an association for the non-synonymous single nucleotide polymorphism within the neuregulin 1 (NRG1) gene, which could also contribute to the risk of SCD.[4,5] Blom et al. suggested that a Brugada pattern was more frequent in patients with schizophrenia (11.6%) compared to controls.[6] The incidence of the Brugada pattern in individuals with schizophrenia is approximately 4%.[7] The extent to which this higher incidence of the Brugada pattern contributes to increased mortality is uncertain, but a 2014 study suggested it could play a role.[8] In addition, polymorphisms or subclinical mutations of the $Na^+$ channel can cause drug-induced long QT syndrome (LQTS) and potentially lead to *Torsades de Pointes*.[9,10]A retrospective cohort study in the United States evaluated the possible correlation between antipsychotic drugs and the incidence of SCD in patients with mental disorders, suggesting that typical and atypical antipsychotics had an adjusted incidence ratio for SCD of 2.00 and 2.27 (1.89–2.73), respectively. Moreover, the risk increased with higher doses. For typical antipsychotics, the risk was 1.31 at low doses and 2.42 at high doses. Among atypical drug users, the ratio increased from 1.59 to 2.86, without any significant difference.[11] Other authors estimated the risk of SCD at 2.9 events per 1000 patient-years and 3.3 events per 1000 patient-years for high-dose treatment.[12]

### *QT interval prolongation: risk factor for* Torsade de Pointes *and SCD*

The association between drug use and QT interval prolongation, leading to potentially fatal cardiac arrhythmias, was first recognized in 1964, when cases of quinidine-induced syncope due to polymorphic ventricular tachycardia were reported.[13] The QT interval represents the time between the onset and the end of ventricular repolarization, which is measured in milliseconds (ms) on the electrocardiogram (ECG).[14,15] In 1966, Francois Dessertenne identified *Torsade de Pointes* (TdP) as a specific form of polymorphic ventricular tachycardia that is invariably preceded by QT interval prolongation and is potentially life-threatening.

The European Society of Cardiology defines a threshold for diagnosing LQTS in symptomatic patients as >500 ms.[16] Above this level, the risk of significant arrhythmia and TdP is high and is considered a threshold for re-evaluating potential pharmacotherapies. Some drugs have been withdrawn due to the unacceptably high risk of ventricular arrhythmias and SCD.[15,17–19] Since 2005, all new drugs with systemic effects have undergone rigorous testing to assess pro-arrhythmic risk before receiving regulatory approval. Although drug-induced QT prolongation has been considered a de facto surrogate biomarker for drug's pro-arrhythmic risk, the risk of SCD and TdP due to drug-induced QT prolongation is also determined by several other factors, such as age, concomitant medications, and associated clinical conditions, such as bradycardia, hypokalemia, hypomagnesemia, ventricular hypertrophy, renal insufficiency, central nervous system disorders, and cardiac disease, as well as the baseline QT/QTc interval.[20,21] Drug-induced QT prolongation occurs when cardiac repolarization is prolonged by alterations in the function of ion channels responsible for potassium ion efflux in phases II and III of the action potential, involving the IKr and IKs currents.[22,23–28]

Drug-induced ion channel blockade is necessary but not the only condition for TdP.[29] The

variable risk of TdP and drug-induced QT prolongation in different individuals has been explained by the concept of "repolarization reserve," which implies that a decrease in the function of any ion channel involved in the repolarization phase of the action potential can remain subclinical if other pathways are intact.[30] Other risk factors for TdP with QT-prolonging drugs include the following: female sex, advanced age, recent conversion from atrial fibrillation with QT-prolonging drugs, concurrent use of multiple drugs that can prolong the QT interval, electrolyte disturbances (hypokalemia, hypomagnesemia, and hypocalcemia), diuretic use, hepatic or renal dysfunction, bradycardia, and occult congenital LQTS or silent mutations in the LQTS genes.[31]

### *Antipsychotic drugs and QT prolongation*

One of the main mechanisms by which antipsychotics increase the risk of SCD is QT prolongation. A recent meta-analysis, which assessed 15 studies covering 15,540 patients with schizophrenia taking antipsychotics, showed that the prevalence of QTc prolongation in this population was about 4.0%.[32] The CATIE study demonstrated that 3% of patients with schizophrenia treated with atypical antipsychotics had QT prolongation.[33] Crediblemeds.org published a table detailing the effects of antipsychotic medications in patients, categorizing them into known risk (droperidol, haloperidol, sulpiride, thioridazine, methadone), conditional risk (risperidone, olanzapine, amisulpride, quetiapine, ziprasidone), and possible risk (clozapine, sertindole, zotepine).[34] Xiong et al. in 2020 collected data from three studies[35–37] on the effects of antipsychotics on the QTc interval, reporting antipsychotics' classification based on QTc prolongation from the highest (thioridazine) to the lowest (perphenazine) risk.[38] A large, real-world study suggests that first-generation antipsychotics have been associated with a greater risk of QT prolongation than second-generation antipsychotics and that antipsychotics with higher hERG affinity are more likely to be associated with QT prolongation.[39]Among patients with long QT, 85.5% had two or more comorbidities such as hypokalemia, human immunodeficiency virus or hepatitis C infection, abnormal T-wave morphology, and methadone treatment. The prevalence of drug-induced long QT interval (500 ms) in patients with schizophrenia treated with antipsychotics has been reported to range from 0.9% to 2.6%.[40,41] For this reason, from 2007 up to now, haloperidol intravenous injection has been contraindicated by most guidelines.[42]

### *Clotiapine*

Clotiapine is a dibenzoepine that interacts with multiple receptors, including the serotonergic and dopaminergic receptors of neurotransmitter systems. Its properties are generally similar to those of the phenothiazine class of neuroleptics (e.g., chlorpromazine), but it also exhibits some properties similar to clozapine (this dibenzoepine presents a similar chemical structure to clotiapine).[43] A review of clotiapine's use[44] documented the possibility of apparent efficacy in patients unresponsive to other typical antipsychotics. Clotiapine clearly induces extrapyramidal syndromes (EPS) like other typical drugs and in this respect differs from clozapine.[45] Clotiapine acts on multiple receptors like clozapine and olanzapine. The ratio of D2 to 5HT2 blockade by clotiapine is similar to that of clozapine.[45–47] By antagonizing dopamine D2 receptors, clotiapine treats the positive psychotic symptoms of schizophrenia. However, D2 antagonism in the basal ganglia can potentially cause dose-related EPS, and cardiac D2 blockade may increase the risk of cardiac arrhythmia. Clotiapine's affinity for 5HT2 receptors treats the negative psychotic symptoms of schizophrenia and can reduce EPS, while selective GABA blockade provides sedative and anxiolytic effects.[45,48–51] Clotiapine has been reported to exacerbate obsessive-compulsive disorder, similar to clozapine.[52–54] This drug is indicated for acute and chronic psychoses, paranoid psychosis, psycho-reactive or neurotic syndromes, and anxiety states. The main side effects are represented by anticholinergic effects, CNS-related dopaminergic effects, orthostatic hypotension, and sialorrhea.[43,55–57] Regarding the cardiac effects and in particular on the QTc, studies report conflicting data.[41,58,59] Despite its widespread use in clinical practice, especially for the pharmacotherapeutic management of agitation,[60] there is insufficient literature on the potential effects of clotiapine on the QTc of treated patients. Given its widespread use in clinical practice and the lack of specific data in the literature, we explored the potential cardiac impact of clotiapine in a naturalistic setting.

The primary objective of this study was to evaluate the potential cardiac effects of clotiapine based on electrocardiographic changes. The secondary objectives were to deepen knowledge on correlations between selected parameters and QTc prolongation in patients treated with clotiapine.

## Methods

### *Study design and setting*

This study design was observational, longitudinal, retrospective, cohort, and single center. The setting was an acute psychiatric ward: Service for Psychiatric Diagnosis and Care (SPDC) in the General Hospital in Baggiovara (Modena).

### *Eligibility criteria*

Inclusion criteria: the cohort consists of subjects over 18 years old admitted to the SPDC in Modena from February 2023 to July 2024. They were prescribed and administered clotiapine and had at least two ECGs performed, the first at admission to the ward or on the same day of clotiapine administration (T0), and the second one after at least 7 days of clotiapine administration (T1). Exclusion criteria: all subjects who were not prescribed clotiapine or were not given any ECG at T0 and T1.

### *Selected variables*

From the medical records of patients included in the study, the following variables were selected:

- Length of hospitalization
- Discharge diagnoses according to ICD-9-CM
- Weight and BMI
- Blood pressure, heart rate, and oxygen saturation were recorded during the hospitalization period
- Comorbid cardiac conditions
- Period of clotiapine treatment
- Clotiapine therapy formulation (oral vs intramuscular)
- Therapies associated with clotiapine
- Combination with other non-psychiatric medications
- Any electrolyte abnormalities
- Toxicology test for substance use screening.

### *Study procedure*

Data relating to clinical and electrocardiographic parameters were collected between February 2023 and July 2024. The data were anonymized before being entered into a database.

We selected all cases of patients hospitalized in our ward during the 6-month study period who were treated with clotiapine and had undergone an ECG and heart rate registration. The QT interval was measured, and QTc interval correction was performed using Bazett's and Fridericia's formula.

We considered: T0, the first day of clotiapine intake, when the first ECG was performed;

T1, the second ECG recorded after 7 days of clotiapine use in the same patient;

T2, the third ECG recorded after 7–21 days of clotiapine use from T1 in the same patient.

At T1 and T2, we recorded the mean dose of clotiapine expressed in mg/day, the number of concomitant psychotropic drugs, the haloperidol combination as concomitant therapy, and the presence or absence of other concomitant psychotropic drugs.

We considered a prolonged QTc interval if it was greater than 500 ms in absolute terms or increased by 60 ms if compared to the previous ECG, in accordance with the European Society of Cardiology.[61]

### *Statistical analysis*

Continuous variables were analyzed as mean and standard deviation, and categorical variables as frequencies. Continuous variables were compared using the $t$ test, and categorical variables were compared using the Pearson chi-square test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the STATA program (StatSoft Inc., Tulsa, OK, USA).

### *Ethical considerations*

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki (version of the 64th WMA General Assembly, Fortaleza, Brazil, October 2013; World Medical Association,

**Table 1.** Psychiatric diagnoses and substance use in our sample.

| Variables | Male ($n=51$) | Female ($n=19$) | Total ($n=70$) | Statistical test Probability |
|---|---|---|---|---|
| Psychiatric diagnosis at discharge (ICD-9-CM), *n* (%) | | | | |
| Schizophrenia spectrum disorders | 39 (76.5%) | 14 (23.5%) | 53 (75.71%) | Pearson $\chi^2=4.98$ $p=0.289$ |
| Organic psychosis | 0 (0%) | 1 (100%) | 1 (1.43%) | |
| Bipolar disorders | 7 (77.8%) | 2 (22.2%) | 9 (12.86%) | |
| Personality disorders | 2 (50%) | 2 (50%) | 4 (5.71%) | |
| Depressive disorders | 3 (100%) | 0 (0%) | 3 (4.29%) | |
| Substance use, *n* (%) | | | | |
| Not present | 25 (67.6%) | 12 (32.4%) | 37 (69.81%) | Pearson $\chi^2=14.90$ $p=0.037$ |
| Cannabinoids | 11 (91.7%) | 1 (8.3%) | 12 (22.64%) | |
| Opiates | 1 (100%) | 0 (0%) | 1 (1.89%) | |
| Cocaine + cannabinoids | 1 (100%) | 0 (0%) | 1 (1.89%) | |
| Methadone + cannabinoids | 2 (100%) | 0 (0%) | 2 (3.77%) | |

2013). It was approved with code 0026032/24 on September 11, 2024 by the Ethics Committee of the Emilia Nord Vast Area (335/2024/OSS/AUSLMO SIRER ID 7668—ClotQTc). The study was subsequently authorized by the Modena AUSL (Decision No. 2847 of 13 November 2024).

We applied the STROBE checklist[62] to control the appropriateness of reporting in the manuscript (Table S1).

## Results

### *Demographic and clinical characteristics of the sample*

We collected an initial sample of 70 patients, 51 males and 19 females, at T0, who were evaluated at T1 ($n=70$) after 1 week. Following, at T2, only 15 patients, 12 males and 3 females, from the initial sample used clotiapine and/or received one ECG. Females were slightly older than males, with a mean age of $43.53 \pm 3.01$ years compared to $36.63 \pm 12.80$ years for males, a marginally significant difference ($p=0.05$); regarding ethnicity, the sample was predominantly Caucasian, with no statistically significant difference between the two sexes ($p=0.323$). Examining other physical parameters, BMI (kg/m$^2$) did not show a statistically significant difference between males ($19.52 \pm 11.94$ $m \pm$ SD) and females ($23.63 \pm 1.48$ $m \pm$ SD; $p=0.41$), blood pressure values were essentially homogeneous between the two sexes, and oxygen saturation (%O2) was consistent across groups. The mean heart rate recorded was slightly higher in females ($86.72 \pm 7.87$ $m \pm$ SD) than in males ($83.49 \pm 5.34$ $m \pm$ SD). Significant electrolyte abnormalities included hyponatremia (two cases, all females) and hypokalemia (five cases, four of which were females), with a significant difference between males and females ($p=0.001$).

As shown in Table 1, regarding the psychiatric diagnoses at discharge of our sample, schizophrenia spectrum disorders accounted for the majority of cases, affecting 75.71% of patients (53 out of 70). Bipolar disorders were diagnosed in 12.86% of cases (9 of 70), followed by personality disorders in 5.71% (4 of 70). At toxicology tests, cannabinoid use was significantly more frequent in males (91.7%, 11 out of 12), confirming a gender-differentiated pattern of substance use, with a male predominance (Table 1).

### *Pharmacological therapy with clotiapine and other drugs*

Regarding pharmacological treatments, only 16.67% of patients had already treated with clotiapine for at least seven previous days before the study period. Oral administration was the most common, involving 98.57% of the sample (69 out of 70). The number of associated pharmacological therapies was slightly higher in females ($2.78 \pm 1.06$ $m \pm$ SD) than in males ($2.24 \pm 1.01$ $m \pm$ SD), with a trend toward significance ($p = 0.06$).

The prescription of haloperidol in combination was prevalent (76.81%; 53 out of 70), with no significant differences between males (74.51%) and females (83.33%; $p = 0.446$). Furthermore, 82.61% of the sample (57 of 70) received other psychotropic medications (including benzodiazepines), with a similar distribution between genders ($p = 0.414$).

Regarding the presence of concomitant non-psychiatric medications, 57.3% of patients (35 of 70) did not receive any concomitant medications. The remaining sample received treatments that included antibiotics (6.56%), anti-hypertensives (13.11%), anticoagulants or antiplatelet drugs (1.64%), and proton pump inhibitors (6.56%). Polypharmacy, defined as the use of more than one of these classes of non-psychiatric medications, was observed in 14.75% of patients (9 of 70), with a slight prevalence in males compared to females (55.6% vs 44.4%; $p = 0.68$).

### *Clotiapine and other drug therapy and ECG/heart rate monitoring in males and females at T1 and T2*

At T1, the mean clotiapine dose (mg/day) administered was $147.36 \pm 85.85$ $m \pm$ SD for the whole sample, with no significant differences between males and females (Table 2). However, differences were underscored in the number of concomitant therapies: 63.16% of females received three or more therapies, compared to 27.45% of males ($p = 0.023$; Table 2).

Haloperidol use was prevalent, with 74.29% of patients receiving this drug, with no significant differences between genders ($p = 0.59$). 84.29% of patients received concomitant psychotropic drugs, including benzodiazepines, with a similar distribution between males (82.35%) and females (89.47%; $p = 0.47$). Regarding electrocardiographic parameters, the mean QTc expressed in ms at T1 was $431.77 \pm 22.49$ ($m \pm$ SD), with values slightly higher in females ($439.32 \pm 18.34$ $m \pm$ SD) than in males ($428.96 \pm 23.39$ $m \pm$ SD; $p = 0.087$). The mean heart rate (bpm) was $78.68 \pm 15.51$ ($m \pm$ SD) for the entire sample, with a slight trend toward higher values in females ($82.25 \pm 9.39$ $m \pm$ SD) compared to males ($77.73 \pm 16.77$ $m \pm$ SD; $p = 0.47$). At T2, the mean clotiapine dose (mg/day) increased to $175.60 \pm 94.99$ ($m \pm$ SD), with a non-significant difference between males and females ($p = 0.054$). Electrocardiographic parameters also showed a mean QTc at T2 of $436.39 \pm 19.87$ ($m \pm$ SD), a slight increase compared to T1, but without reaching statistical significance ($p = 0.11$). The mean heart rate (bpm) at T2 was $85.26 \pm 13.46$ ($m \pm$ SD), a marginally significant difference from T1 ($p = 0.06$). Females continued to receive a greater number of combination therapies (100% with three or more drugs) than males (30.77%; $p = 0.09$). Haloperidol use was also significantly higher in males (100%) than females (66.67%; $p = 0.03$; Table 2). Regarding the difference in the QTc interval (ms) between time points T1 and T2 (which has a minimum duration of 7 days and a maximum of 21 days), a slight mean increase was observed in both males ($5.12 \pm 23.72$ $m \pm$ SD) and females ($3.26 \pm 22.40$ $m \pm$ SD), with an overall value of $4.61 \pm 23.23$ ($m \pm$ SD), without any statistically significant difference ($t = 0.29$; $p = 0.77$; $t$ test). The change in heart rate (bpm) between T1 and T2 showed a mean increase in males of $5.40 \pm 17.98$ ($m \pm$ SD) and in females of $11.00 \pm 9.13$ ($m \pm$ SD), with an overall value of $6.58 \pm 16.57$ ($m \pm$ SD), with greater increase in females than in males, without any statistically significant difference ($t = -0.85$; $p = 0.40$; $t$ test).

### *Comparison between the follow-ups*

In Table 3, the mean QTc values ($m \pm$ SD) between T0, T1, and T2 are shown. In the comparison between T0 and T1, the mean QTc (ms), evaluated through Bazett's formula, increased from $431.79 \pm 22.49$ ($m \pm$ SD) to $436.37 \pm 19.78$ ($m \pm$ SD), showing a mean increase of $4.59 \pm 22.90$ ($m \pm$ SD), equal to a change of 1.1%. Despite this slight increase, it was not statistically significant ($p = 0.0984$). Comparing T1 and T2 in 15 individuals, the mean QTc (ms)

**Table 2.** Treatment with clotiapine at T1 and T2 in males and females.

| Variables | Male | Female | Total | Statistical test Probability |
|---|---|---|---|---|
| **T1** | ***n*** **= 51** | ***n*** **= 19** | ***n*** **= 70** | |
| Clotiapine dose, mg | | | | |
| *m* ± SD | 149.62 ± 86.97 | 141.28 ± 84.78 | 147.36 ± 85.85 | $t = 0.359$; $p = 0.720$ |
| Number of associated drugs, *n* (%) | | | | |
| 1 | 12 (23.53%) | 2 (10.53%) | 14 (20%) | Pearson $\chi^2 = 7.59$; $p = 0.023$ |
| 2 | 25 (49.02%) | 5 (26.32%) | 30 (42.86%) | |
| 3 or more | 14 (27.45%) | 12 (63.16%) | 26 (37.14%) | |
| Haloperidol in combination, *n* (%) | | | | |
| Not present | 14 (27.45%) | 4 (21.05%) | 18 (25.71%) | Pearson $\chi^2 = 0.30$; $p = 0.59$ |
| Present | 37 (72.55%) | 15 (78.95%) | 52 (74.29%) | |
| Other associated psychotropic drugs, *n* (%) | | | | |
| Not present | 9 (17.65%) | 2 (10.53%) | 11 (15.71%) | Pearson $\chi^2 = 0.53$; $p = 0.47$ |
| Present | 42 (82.35%) | 17 (89.47%) | 59 (84.29%) | |
| QTc | | | | |
| *m* ± SD | | | | |
| Bazett's formula | 428.96 ± 23.39 | 439.32 ± 18.34 | 431.77 ± 22.49 | $t = -1.74$; $p = 0.087$ |
| Fridericia's formula | 412 ± 17.49 | 415.51 ± 19.83 | 412.93 ± 18.05 | $t = -0.70$; $p = 0.4837$ |
| Heart rate | | | | |
| *m* ± SD | 77.73 ± 16.77 | 82.25 ± 9.39 | 78.68 ± 15.51 | $t = -0.73$; $p = 0.47$ |
| **Variables** | **Male** | **Female** | **Total** | **Statistical test Probability** |
| **T2** | **(*n* = 12)** | **(*n* = 3)** | **(*n* = 15)** | |
| Clotiapine dose, mg | | | | |
| *m* ± SD | 150.5546 | 284.1267 | 175.5994 | $t = -2.101$; $p = 0.054$ |
| Number of associated drugs, *n* (%) | | | | |
| 1 | 2 (15.38%) | 0 (0%) | 2 (12.5%) | Pearson $\chi^2 = 4.75$; $p = 0.09$ |
| 2 | 7 (53.85%) | 0 (0%) | 7 (43.75%) | |
| 3 or more | 4 (30.77%) | 3 (100%) | 7 (43.75%) | |

*(Continued)*

**Table 2.** (Continued)

| Variables | Male | Female | Total | Statistical test Probability |
|---|---|---|---|---|
| T2 | (*n* = 12) | (*n* = 3) | (*n* = 15) | |
| Haloperidol in combination, *n* (%) | | | | |
| Not present | 0 (0%) | 1 (33.33%) | 1 (6.25%) | Pearson $\chi^2 = 4.62$; $p = 0.03$ |
| Present | 13 (100%) | 2 (66.67%) | 15 (93.75%) | |
| Other associated psychotropic drugs, *n* (%) | | | | |
| Not present | 2 (15.38%) | 0 (0%) | 2 (12.5%) | Pearson $\chi^2 = 0.53$; $p = 0.47$ |
| Present | 11 (84.62%) | 3 (100%) | 14 (87.5%) | |
| QTc, $m \pm SD$ | | | | |
| Bazett's formula | $434.08 \pm 20.32$ | $442.58 \pm 17.65$ | $436.39 \pm 19.87$ | $t = -1.61$; $p = 0.11$ |
| Fridericia's formula | $403.66 \pm 24.41$ ($n = 11$) | 428.69 ($n = 1$) | 405.75 | |
| Heart rate | | | | |
| $m \pm SD$ | $83.13 \pm 13.90$ | $93.25 \pm 8.10$ | $85.26 \pm 13.46$ | $t = -1.96$; $p = 0.06$ |

decreased slightly, from $432.13 \pm 21.59$ ($m \pm SD$) to $430.94 \pm 24.49$ ($m \pm SD$), with a mean difference of $-1.19 \pm 26.45$ ms, equivalent to a negative change of 0.3%. Again, the reduction was not significant ($p = 0.8599$).

In the comparison between T0 and T1, the mean QTc (ms), evaluated by means of Fridericia's formula, changed from $412.93 \pm 18.05$ ($m \pm SD$) to $412.49 \pm 17.67$ ($m \pm SD$), showing a reduction of $-0.44$ ms $\pm -0.38$ ($m \pm SD$), equal to a change of $-0.1$%, without any statistically significant difference ($t = 0.19$; $p = 0.8511$; $t$ test). Comparing T1 and T2, in 15 individuals, the mean QTc (ms) decreased slightly, from $407.80 \pm 17.64$ ($m \pm SD$) to $405.75 \pm 24.37$ ($m \pm SD$), with a mean difference of $-2.05 \pm 6.72$ ms, equivalent to a negative change of $-1$%. Again, the reduction was not significant ($t = 0.42$; $p = 0.6788$; $t$ test).

The percentile distribution of QTc interval changes (Figure 1) between time T0 and time T1 shows that, at the 50th percentile (median), the QTc (Bazett's formula) increase was 3.5 ms. Subjects with an increase equal to or greater than the median ($M = 3.5$) of QTc increase at T1 accounted for half of the sample, but only 0.7% (only one patient) had an increase greater than 60 ms.

We did not observed any statistically significant difference of the clotiapine dose between the two follow-ups, but we reported the following statistically significant differences between T1 and T2: the number of associated drugs (Pearson $\chi^2 = 18.04$; $p = 0.001$); haloperidol in combination (Pearson $\chi^2 = 63.71$; $p = 0.000$); other associated psychotropic drugs (Pearson $\chi^2 = 62.16$; $p = 0.000$; Table 3).

## Discussion

This naturalistic study investigated the effects of clotiapine on electrocardiographic parameters in a sample of individuals admitted to the Psychiatric Service for Diagnosis and Care in Modena. The primary objective of the study was to evaluate the potential cardiac effect of clotiapine on QTc prolongation, which was evaluated through a retrospective longitudinal analysis. Furthermore, the demographic and clinical characteristics of the sample were assessed, as well as any correlations between QTc prolongation and selected cardiovascular and pharmacological parameters in patients treated with clotiapine.

The analysis of demographic and clinical characteristics highlighted some significant differences

**Table 3.** Comparison of QTc, heart rate, clotiapine dose, and other associated drugs between T0, T1, and T2..

| Variables | T0 ($n = 70$) | T1 ($n = 70$) | T2 ($n = 15$) | Statistical test Probability |
|---|---|---|---|---|
| QTc, $m \pm SD$ | | | | |
| ms (Bazett's formula) | 431.77 ± 22.49 | 436.39 ± 19.87 | | T0 vs T1<br>$t = -1.66$, $p = 0.1010$, $t$ test |
| T0–T1, $\Delta m \pm SD$ (%) | | 4.61 ± 23.22 (1.07%) | | |
| | | | 431.00 ± 25.34 | T1 vs T2<br>$t = 0.61$, $p = 0.5544$, $t$ test |
| T1–T2, $\Delta m \pm SD$ (%) | | −5.39 ± 23.02 (−1.24%) | | |
| ms (Fridericia's formula) | 412.93 ± 18.05 | 412.49 ± 17.67 | | T0 vs T1<br>$t = 0.19$, $p = 0.0984$, $t$ test |
| T0–T1, $\Delta m \pm SD$ (%) | | −0.44 ms ± −0.38 (−0.1%) | | |
| | | | 405.75 ± 24.37 | T1 vs T2<br>$t = 0.42$, $p = 0.6788$, $t$ test |
| T1–T2, $\Delta m \pm SD$ (%) | | −2.05 ± 6.72 (−1%) | | |
| Heart rate, $m \pm SD$ | | | | |
| bpm | 78.68 ± 15.51 | 85.26 ± 13.46 | 95.87 ± 9.34 | T0 vs T1<br>$t = -2.4480$, $p = 0.0192$, $t$ test<br>T1 vs T2<br>$t = -1.812$, $p = 0.1129$, $t$ test |
| Clotiapine dose, $m \pm SD$ | | | | |
| mg | | 147.36 ± 85.85 | 175.60 ± 09.98 | T1 vs T2<br>$t = 1.10$, $p = 0.2878$, $t$ test |
| Number of associated drugs, $n$ (%) | | | | |
| 1 | | 14 (20%) | 1 (6.7%) | T1 vs T2<br>Pearson $\chi^2 = 18.04$, $p = 0.001$ |
| 2 | | 30 (42.86%) | 7 (46.7%) | |
| 3 or more | | 26 (37.14%) | 7 (46.7%) | |
| Haloperidol in combination, $n$ (%) | | | | |
| Not present | | 18 (25.71%) | 1 (6.7%) | T1 vs T2<br>Pearson $\chi^2 = 63.71$, $p = 0.000$ |
| Present | | 52 (74.29%) | 14 (93.3%) | |
| Other associated psychotropic drugs, $n$ (%) | | | | |
| Not present | | 11 (15.71%) | 1 (13.3%) | T1 vs T2<br>Pearson $\chi^2 = 62.16$, $p = 0.000$ |
| Present | | 59 (84.29%) | 14 (93.3%) | |

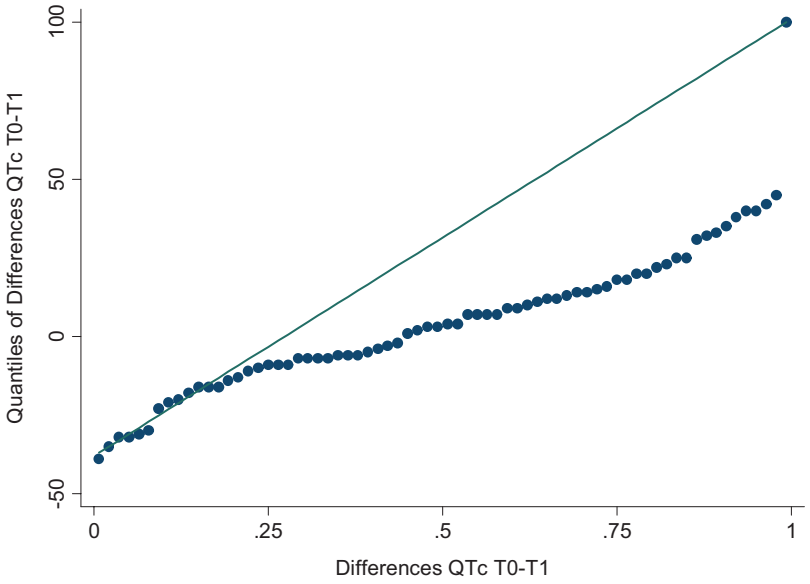


**Figure 1.** Differences of QTc between T0 and T1 in all participants ($n = 70$).

between the two sexes. Females had a higher mean age than males, which may reflect the more frequent late-onset schizophrenia spectrum disorders in females[63] or, as suggested by the literature, different rates of health care utilization by males and females.[6] Another difference between the two sexes is heart rate, which is slightly higher in females than in males, which may reflect greater autonomic sensitivity, as reported by some authors,[2] who highlight reduced parasympathetic activity in women with psychiatric conditions. Females in our sample also had a higher frequency of cardiac comorbidities, although this difference was not statistically significant. This trend may be relevant, considering that female gender is a known independent risk factor for QTc prolongation.[31,64]

Schizophrenia spectrum disorders constitute the majority of diagnoses at discharge in our sample. This finding is consistent with the literature showing that patients with schizophrenia are often treated with antipsychotic medications, including clotiapine,[43] often at high doses and in combination, indirectly suggesting the complexity and severity of these patients' conditions. Our data show significantly higher substance use in males than in females, as confirmed in the literature.[65] The high rate of substance use, particularly in males, highlights the importance of considering addictions as an additional risk factor for QTc prolongation in antipsychotic treatments.[66]

The different sample sizes of the two follow-up periods, with few individuals of the original sample at T2 in comparison to T1, could be interpreted as the use of clotiapine in urgent and acute clinical situations as a sedative drug for agitation, as suggested by the literature.[60] This observation may be further supported by the data that only 16.67% of subjects were receiving clotiapine therapy during the 7 days before the study, indicating its use primarily as an emergency medication in an acute hospital setting although its predominantly oral administration could reflect a clinical practice of favoring patient adherence. The greater number of combination therapies suggests a more intensive therapeutic approach, which may reflect greater clinical severity and complexity. The widespread use of haloperidol as a combination therapy highlights a pharmacological strategy aimed at the immediate control of acute symptoms. Co-administration of clotiapine and haloperidol did not appear to result in a significant increase in cardiac risk (observed through an increase in QTc), confirming the safety profile of clotiapine even in combination.

Monitoring of electrocardiographic parameters during clotiapine therapy shows limited changes in QTc and heart rate. At T0, the mean QTc remains within the physiological limits of this parameter, and the subsequent increase at T1 as well as at T2 was limited, supporting the safety profile of clotiapine compared to other

antipsychotics known to prolong the QTc, as highlighted by other authors.[38]

The differences between the two sexes, with QTc values generally higher in females, are consistent with what has been historically described in the literature.[64,67] However, in our sample, we did not detect any significant changes in QTc variation between the two sexes, confirming the absence of a significant impact of clotiapine on QTc.

It is interesting to note that the percentage change in QTc at the different measurement times is positive between T0 and T1 and tends to become negative between T1 and T2 and, even more so, between T2 and T3. This clinical finding, although limited by the different sample sizes at the three follow-ups, could highlight a tolerance phenomenon to the QTc-prolonging in continuous use of this drug. On the contrary, heart rate showed a tendency to increase during treatment, reflecting an activation of autonomic response, as usual in acute psychiatric conditions.[68]

The percentage distribution of QTc differences between T0 and T1 shows that the majority of patients exhibited modest or no increase, further confirming the absence of a clinically relevant risk. In fact, we observed only one patient at T1 with an increase greater than 60 ms compared to T0, which, however, did not reach the critical QTc prolongation $\geqslant$500 ms. The maximum increase of 100 ms observed in this single patient (representing 0.7% of all patients between T0 and T1) is below the prevalence rate of QTc prolongation induced by psychotropic drugs, which in the literature ranges between 0.9% and 3%.[41,69]

In light of our study, we emphasize that ECG measurements must be monitored to ensure accurate assessment of drug-induced QT prolongation. Early identification of QTc alterations and associated risk factors during treatment may help reduce cardiac morbidity and mortality in patients treated with antipsychotic drugs. Furthermore, accurate ECG measurements could help provide a more detailed understanding of the risk of SCD associated with each antipsychotic drug and, simultaneously, implement personalized pharmacological treatment.[70] Although individual genetic factors and age are considered the main determinants of the QT interval, as highlighted by many authors,[71,72] careful clinical analysis of drug treatment as an additional but avoidable risk factor for QT prolongation may reduce cardiac arrhythmias due to antipsychotic treatment. A relatively safe drug for QTc interval prolongation, even in combination with other antipsychotics, such as clotiapine, could represent an important and effective therapeutic tool to be used especially in emergency situations where cardiac monitoring is not available and characterized by psychiatric agitation for rapid patient tranquilization.

## Limitations

Our study has some limitations:

- The sample size is limited; it is composed of 70 patients at T1 and subsequently reduced to only 15 patients at T2 due to many participants dropping out as the timing of the ECG did not always match our study's inclusion criteria. This could lead to attrition bias, potentially overestimating or underestimating the results.
- This study is single center, and the sample is predominantly Caucasian, consistent with the ethnic distribution of the local population. These characteristics may limit the generalization of the study results.
- All patients were using concomitant medications; ideally, patients would have been taking only clotiapine, but our sample was observational and naturalistic.

Some limitations include the monocentric and retrospective nature of the study, combined with the limited sample size, which restricts the generalizability of the data obtained. Furthermore, the lack of a control group with untreated patients or the presence of concomitant pharmacotherapies in all patients partially limits the possibility of specifically attributing the observed effects to clotiapine.

The advantages of this study include both the contribution of scientific knowledge and the safe use in clinical practice of clotiapine treatment alone or also in combination with other drugs that can potentially lead to QT interval alterations. It also represents a report from a real-world clinical setting, which can be developed in further study with lager sample and non-naturalistic design.

## Conclusion

Our results suggest that QTc prolongation, which was reported in a very small number of patients, remained within acceptable limits and did not significantly reach high clinical risk thresholds. This finding is particularly significant given the frequent use of clotiapine, often in combination with other psychotropic drugs, such as haloperidol, which can amplify the risk of QTc prolongation. Another important point emerging from this study concerns the stabilization of electrocardiographic parameters over time, suggesting a possible adaptation or tolerance effect to the QTc effects of clotiapine. The results obtained in this study are preliminary and represent an initial confirmation of an empirical finding. Further prospective research, conducted on larger samples, in multicenter settings, will be necessary to confirm and further explore this topic. In conclusion, the study contributes to a better understanding of the use of clotiapine in clinical practice, highlighting its safety profile. Finding a safe and universally accepted protocol for prescribing antipsychotics remains a persistent challenge in medicine. Predictive models that integrate clinical history with demographic and ECG characteristics can help estimate an individual's susceptibility to therapy-associated risks, including QTc prolongation.

## Declarations

### *Ethics approval and consent to participate*

It was approved with code 0026032/24 on 11 September 2024 by the Ethics Committee of the Emilia Nord Vast Area (335/2024/OSS/AUSLMO SIRER ID 7668—ClotQTc). The study was subsequently authorized by the Modena AUSL (Decision No. 2847 of 13 November 2024). Consent to participate was not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Rosaria Di Lorenzo:** Conceptualization; Formal analysis; Investigation; Methodology; Software; Supervision; Writing – original draft; Writing – review & editing.

**Andrea Santoro:** Conceptualization; Data curation; Investigation; Writing – original draft.

**Jessica Bonisoli:** Data curation; Investigation; Writing – original draft.

**Carolina Bottone:** Data curation; Methodology; Software; Writing – original draft.

**Paola Ferri:** Conceptualization; Supervision; Validation; Writing – review & editing.

**Sergio Rovesti:** Conceptualization; Validation; Writing – review & editing.

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### *Competing interests*

The authors declare that there is no conflict of interest.

### *Availability of data and materials*

Not applicable.

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## Supplemental material

Supplemental material for this article is available online.

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