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Published in:
CNS Spectrums

DOI:
10.1017/S1092852917000402

Publication date:
2018

Document version
Accepted manuscript

Citation for published version (APA):
Elliott, A. F., Johan Mørk, T., Højlund, M., Christensen, T., Jeppesen, R., Madsen, N., ... Munk-Jørgensen, P. (2018). QTc interval in patients with schizophrenia receiving antipsychotic treatment as monotherapy or polypharmacy. CNS Spectrums, 23(4), 278-283. https://doi.org/10.1017/S1092852917000402

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QTc interval in patients with schizophrenia receiving antipsychotic treatment as monotherapy or polypharmacy

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Abstract

Antipsychotics are associated with the polymorphic ventricular tachycardia, torsades de pointes, which, in the worst case, can lead to sudden cardiac death. The QT interval corrected for heart rate (QTc) is used as a clinical proxy for torsades de pointes. The QTc interval can be prolonged by antipsychotic monotherapy, but it is unknown if the QTc interval is prolonged further with antipsychotic polypharmaceutical treatment. Therefore, this study investigated the associations between QTc interval and antipsychotic polypharmaceutical treatment in schizophrenia and measured the frequency of QTc prolongation among patients. We carried out an observational cohort study of unselected patients with schizophrenia visiting outpatient facilities in the Region of Central Jutland, Denmark. Patients were enrolled from January 2013 to June 2015, with follow-up until June 2015. Data were collected from clinical interviews and clinical case records. Electrocardiograms were available for 65 patients and 6% had QTc prolongation. We observed no difference in average QTc interval for the whole sample of patients receiving no antipsychotics, antipsychotic monotherapy or antipsychotic polypharmaceutical treatment (p=0.29). However, women presented with a longer QTc interval when receiving polypharmacy than when receiving monotherapy (p=0.01). In conclusion, we recommend an increased focus on monitoring the QTc interval in women with schizophrenia receiving antipsychotics as polypharmacy.
Introduction

Patients with schizophrenia die more frequently from sudden cardiac death than the general population.\(^1\) Antipsychotics are suggested as one of the causes of increased risk of sudden cardiac death.\(^2\) In fact, antipsychotics are associated with a threefold increase in risk of sudden cardiac death.\(^3\) Cardiac death can be caused by several mechanisms. In particular, the fatal polymorphic ventricular tachycardia, torsades de pointes (TdP), is associated with some antipsychotics.\(^4\) TdP is rare and cannot be predicted, but prolongation of the QT interval corrected for heart rate (QTc) serves as a risk factor for TdP and is used as a proxy for TdP in clinical practice.\(^5\)

Both typical and atypical antipsychotics have been associated with prolonged QTc interval when used as monotherapy.\(^6,7\) It has become common to use antipsychotic polypharmacy in the treatment of schizophrenia.\(^8\) However, because of contradictory evidence, it is uncertain whether antipsychotic polypharmacy prolongs the QTc interval more than antipsychotic monotherapy.\(^9-11\) A recent meta-analysis did not find an increased QTc interval in patients with schizophrenia treated with antipsychotics, but the evidence available is scarce and inconsistent.\(^11\)

The aim of the present study was to investigate for associations between QTc interval and antipsychotic monotherapy and polypharmaceutical treatment, and whether monotherapy and polypharmacy relates to the dose of antipsychotics.

Methods

Design
The study was a prospective, dual-center, naturalistic study of unselected patients with schizophrenia visiting outpatient facilities. The study is part of an interventional quality-assurance project to prevent early death from somatic causes in patients with mental illness.\(^12\)

Sample
Inclusion criteria
Patients diagnosed with schizophrenia according to the ICD-10 research criteria were included.\(^13\) Patients were recruited from two psychiatric outpatient clinics in the central region of Denmark, Regional Hospital Herning and Regional Hospital Randers. Both facilities treated first-ever diagnosed patients, aged 18–45 years, in an intensive 2-year treatment program.\(^14\) The patients were enrolled consecutively from January 2013 to June 2015.

Patients with chronic schizophrenia treated at the Regional Psychiatry West, who were diagnosed at least 2 years prior to the start of the project, were also included.

Data
Demographic and clinical characteristics.
Data on age, sex, height, weight, blood pressure, tobacco use, heart rate, illness duration, diabetes medicine, heart medication, antidepressants, mood stabilizers and antipsychotic drugs were collected, along with clinical activity, and registered into a research database. Illness duration was defined as the time between first-ever contact with psychiatric
healthcare, regardless of diagnosis and the date of interview. Doses of antipsychotic drugs were transformed into defined daily dose (DDD).15

Electrocardiogram
A standard 12-lead paper electrocardiogram (ECG) was recorded at 25 mm/s and then scanned (HP Scanjet G3110) at 600 dpi. Using an on-screen caliper the ECG was analyzed at a magnification of 800%. To eliminate interobserver variability the analyses were performed by a single observer (TC). The QT interval was measured from the onset of the QRS complex to the offset of the T-wave, defined as the deflection of the T-wave where it returns to the isoelectric line, or as the nadir between the T and U wave. The QT-interval was measured in three successive beats in lead II, and a mean QT was calculated. Fredericia’s formula (QT/RR^{1/3}) was used to calculate the QTc, and the measurement was corrected for time of day. QTc prolongation was defined as a QTc interval longer than 440 ms. The PR interval and the QRS duration were calculated as the mean of measurements in three beats in lead II.

Statistical analysis
Descriptive statistics regarding the patients’ characteristics were calculated with index data for all participants. Mean values for QTc and DDD were stratified by the number of antipsychotics were examined and compared. Analyses of descriptive statistics were done using one of three methods: (1) for normally distributed data either a t-test (Welch’s t-test) or an ANOVA was used to determine differences; (2) for non-normal data either Wilcoxon’s rank sum or Kruskal–Wallis test was used; (3) for hypotheses regarding proportions, a test for equal proportions was used to determine differences in the proportion, for example the proportion of females are the same in all antipsychotic groups.

For women, association between QTc, DDD and number of antipsychotics with either monotherapy or polypharmacy was studied using an initial linear regression. However, DDD was an insignificant variable and therefore removed.

All calculations were done using STATA version 12.1 (StataCorp, College Station, TX, USA) and R version 3.1.1.

Ethics
The Danish Research Ethics Committee (Central Region) approved the study as a quality-assurance study of the departments, cf. law 593, §2 No.1, enquiry 197/2012. The study was approved by The Danish Data Protection Agency (2007-58-0010).

Results
ECGs were available in 65 patients. Seven patients received no antipsychotic drugs, 39 received one antipsychotic drug (monotherapy) and 19 received two or more different antipsychotics (polypharmacy). There were no significant differences between patients receiving no antipsychotics, monotherapy or polypharmacy with regard to to sex, age, body mass index, heart rate, blood pressure and number of cigarettes smoked daily (Table 1). However, the number of patients who smoked varied; 86% patients in the no antipsychotic group smoked, while only 59% and 66% smoked in the monotherapy group and the polypharmacy group, respectively. Patients treated with antipsychotic monotherapy had a significantly increased length of illness compared with the groups
receiving no antipsychotics (p=0.039) and antipsychotic polypharmacy (p=0.033). None of the 65 patients received any cardiac medication. Furthermore, there were two patients with diabetes in the group receiving antipsychotic monotherapy and one patient with diabetes in the antipsychotic polypharmacy group.

One patient in the no antipsychotics group and one patient in the monotherapy group had a QTc interval longer than 440 ms, and three patients in the polypharmacy group had a QTc interval longer than 440 ms. According to QRS duration and PR interval no significant difference between the groups was found.

Women in the group receiving antipsychotic polypharmacy presented with longer QTc intervals than the women in the group receiving antipsychotic monotherapy (p=0.010), while no such difference was observed in men (p=0.917) (Figure 1).

We found a significantly (p=0.025) higher DDD of antidepressant drugs in patients receiving antipsychotic polypharmacy (mean DDD 1.57) than patients receiving antipsychotic monotherapy (mean DDD 0.74). However, the DDD of antidepressant drugs did not influence the QTc interval in women (p=0.80).

No significant increase in DDD of antipsychotics was observed in patients receiving multiple antipsychotics compared with patients receiving a single antipsychotic drug or no antipsychotics at all (Figure 2)

Discussion

In the current study the frequency of patients with a QTc interval longer than 440 ms was 6%. Only among women did we observe a significantly increased QTc interval when treated with antipsychotic polypharmacy compared with antipsychotic monotherapy. No such increase in QTc was found in men. The dose of antipsychotics did not increase when the patients received multiple antipsychotic drugs, compared with the dose of antipsychotic in patients receiving only one type of antipsychotic.

A previous study found that 20% of patients with schizophrenia had QTc prolongation with a QTc interval above 450 ms.\textsuperscript{10} This is a high proportion compared with the findings of the present study, where only 6% of patients had a QTc interval longer than 440 ms. This may be owing to that fact that the two outpatient facilities followed safety recommendations with regard to prolonged QTc interval, which may have led to a selection of individuals without a great number of ECG abnormalities. Other studies have reported a prevalence rate for QTc prolongation of between 2% and 3.5% of patients with schizophrenia, but the threshold for QTc prolongation in these studies was a QTc interval above 500 ms.\textsuperscript{16,17}

In our study antipsychotic polypharmacy did not increase the dose of antipsychotics, compared with antipsychotic monotherapy. This is in contrast to a study by Barbui et al., which found that antipsychotic polypharmacy is associated with prolongation of the QTc interval, and that this effect is mediated by antipsychotic dose.\textsuperscript{9}

In addition to antipsychotics, numerous risk factors may increase QTc interval, among which are antidepressant medication and mood stabilizers such as lithium.\textsuperscript{18} In this study we observed no difference in the use of mood stabilizers between the three groups.
However, there was a significant increase of DDD of antidepressant medication in patients in the antipsychotic polypharmacy group. In our cohort, there was no difference in QTc interval with different use of antidepressants.

The QTc interval increases with older age and therefore age is also considered a risk factor. In this study age was not taken into account as age was very similar in the three groups of patients we compared. Women with a psychiatric illness, receiving psychotropic medication have an increased risk of QTc prolongation. This is in accordance with our present findings. It is well described that women are at increased risk of prolonged QTc with QTc-prolonging drugs.

The study has some limitations. Firstly, two centers were involved in the study and therefore different ECG recording devices were used. Although the ECGs were recorded digitally, there were logistical difficulties in analyzing the ECGs directly on screen at both centers. Therefore, the ECGs had to be printed and sent to a location where all the ECGs were scanned electronically. We cannot dismiss the fact that some resolution and accuracy of the ECGs could have been lost. However, it is not likely that the results with respect to QTc interval would have changed much with digital analysis.

Secondly, prior studies have shown that an increased QTc interval seems to differ markedly among different antipsychotics, for example thioridazine ziprasidone and sertindole increase QTc interval more than haloperidol, olanzapine, quetiapine and risperidone. This has not been taken into account in the current study. This study has merely investigated the overall effect of antipsychotics when given as either monotherapy or polypharmacy in routine clinical practice.

Among the strengths of the study is that we included otherwise non-selected patients from routine clinical practice in two centers.

**Conclusion**

Only 6% of patients with schizophrenia showed QTc prolongation during antipsychotic drug treatment. Women had increased QTc intervals when treated with two or more types of antipsychotics versus treatment with a single antipsychotic, which may indicate that women are at increased risk of TdP. We recommend an increased focus on monitoring of the QTc interval in women with schizophrenia receiving antipsychotics as polypharmacy.

**References**


Table 1: Demographic and clinical features of patients with schizophrenia (N = 65) treated with no, one (monotherapy), or two or more (polypharmacy) antipsychotics (mean ± SD unless otherwise indicated)

<table>
<thead>
<tr>
<th></th>
<th>No antipsychotics</th>
<th>Antipsychotic monotherapy</th>
<th>Antipsychotic polypharmacy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n)</td>
<td>2</td>
<td>17</td>
<td>8</td>
<td>0.758</td>
</tr>
<tr>
<td>Men (n)</td>
<td>5</td>
<td>22</td>
<td>11</td>
<td>0.758</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29 ± 10</td>
<td>29 ± 10</td>
<td>29 ± 9</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>Length of illness, year (years)</td>
<td>2 ± 3</td>
<td>6 ± 7</td>
<td>4 ± 6</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 5</td>
<td>28 ± 8</td>
<td>31 ± 8</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=18)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 12</td>
<td>88 ± 18</td>
<td>83 ± 11</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>(n=5)</td>
<td>(n=35)</td>
<td>(n=16)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, systolic (mmHg)</td>
<td>130 ± 8</td>
<td>124 ± 13</td>
<td>129 ± 11</td>
<td>0.290</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=33)</td>
<td>(n=17)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, diastolic (mmHg)</td>
<td>82 ± 9</td>
<td>82 ± 9</td>
<td>87 ± 5</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=33)</td>
<td>(n=17)</td>
<td></td>
</tr>
<tr>
<td>Tobacco (daily no. of cigarettes smoked)</td>
<td>14 ± 14</td>
<td>16 ± 7</td>
<td>16 ± 9</td>
<td>0.532</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=23)</td>
<td>(n=12)</td>
<td></td>
</tr>
<tr>
<td>Dose of antipsychotics (mean DDD)</td>
<td>0</td>
<td>1.60 ± 1.28</td>
<td>2.03 ± 1.28</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>Antidepressant drugs (mean DDD)</td>
<td>0.74 ± 1.02</td>
<td>0.74 ± 1.12</td>
<td>1.57 ± 1.59</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>Mood stabilizers (mean DDD)</td>
<td>0.20 ± 0.38</td>
<td>0.21 ± 0.61</td>
<td>0.23 ± 0.45</td>
<td>0.607</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>QTc &gt;440 ms (n)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.163</td>
</tr>
<tr>
<td>QTc interval mean (ms)</td>
<td>401 ± 22</td>
<td>391 ± 23</td>
<td>399 ± 29.85</td>
<td>0.381</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>QTc interval, women (ms)</td>
<td>391 ± 8</td>
<td>395 ± 17</td>
<td>417 ± 24</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>(n=2)</td>
<td>(n=17)</td>
<td>(n=8)</td>
<td></td>
</tr>
<tr>
<td>QTc interval, men (ms)</td>
<td>405 ± 25</td>
<td>387 ± 28</td>
<td>386 ± 28</td>
<td>0.418</td>
</tr>
<tr>
<td></td>
<td>(n=5)</td>
<td>(n=22)</td>
<td>(n=11)</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>84 ± 16</td>
<td>88 ± 23</td>
<td>83 ± 17</td>
<td>0.746</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>168 ± 21</td>
<td>151 ± 26</td>
<td>153 ± 19</td>
<td>0.240</td>
</tr>
<tr>
<td>(n=7)</td>
<td>(n=39)</td>
<td>(n=19)</td>
<td></td>
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</table>
Figure 1: Correlation of number of antipsychotics and QT interval corrected for heart rate (QTc) in patients with schizophrenia (men, n = 38; women, n = 27). Men and women were divided into three groups: one group received no antipsychotics, one group received one antipsychotic (monotherapy), and the other received two or more antipsychotics (polypharmacy).
Figure 2: Correlation of number of antipsychotics and defined daily dose (DDD) of antipsychotics in patients with schizophrenia (men, n = 38; women, n = 27). Men and women were divided into three groups; one group received no antipsychotics, one group received one antipsychotic (monotherapy), and the other received two or more antipsychotics (polypharmacy).