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ORIGINAL ARTICLE

Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study

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Aims. In recent years several warnings have been issued by regulatory authorities on the risk of electrocardiogram abnormalities in individuals exposed to psychotropic drugs. As a consequence of these warnings, monitoring of the QT interval corrected for heart rate (QTc) has become increasingly common. This study was conducted to measure the frequency of QTc prolongation in unselected psychiatric patients, and to document the associated factors using a cross-sectional approach.

Method. The study was carried out in 35 Italian psychiatric services that are part of the STAR (*Servizi Territoriali Associati per la Ricerca*) Network, a research group established to produce scientific knowledge by collecting data under ordinary circumstances. During a three-month period, a consecutive unselected series of both in- and out-patients were enrolled if they performed an ECG during the recruitment period and were receiving psychotropic drugs on the day ECG was recorded.

Results. During the recruitment period a total of 2411 patients were included in the study. The prevalence of QTc prolongation ranged from 14.7% (men) and 18.6% (women) for the cut-off of 450 ms, to 1.26% (men) and 1.01% (women) for the cut-off of 500 ms. In the multivariate model conducted in the whole sample of patients exposed to psychotropic drugs, female sex, age, heart rate, alcohol and/or substance abuse, cardiovascular diseases and cardiovascular drug treatment, and drug overdose were significantly associated with QTc prolongation. In patients exposed to antipsychotic drugs, polypharmacy was positively associated with QTc prolongation, whereas use of aripiprazole decreased the risk. In patients exposed to antidepressant drugs, use of citalopram, citalopram dose and use of haloperidol in addition to antidepressant drugs, were all positively associated with QTc prolongation.

Conclusions. The confirmation of a link between antipsychotic polypharmacy and QTc prolongation supports the current guidelines that recommend avoiding the concurrent use of two or more antipsychotic drugs, and the confirmation of a link between citalopram and QTc prolongation supports the need for routine QTc monitoring. The relatively low proportion of patients with QTc prolongation not only suggests compliance with current safety warnings issued by regulatory authorities, but also casts some doubts on the clinical relevance of QTc prolongation related to some psychotropic drugs.

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Key words: Antidepressant, antipsychotic, adverse effect, psychotropic drugs.

Background

In recent years several warnings have been issued by regulatory authorities on the risk of electrocardiogram (ECG) abnormalities among individuals exposed to psychotropic drugs (Meyer-Massetti *et al.* 2010; Kogut *et al.* 2013). In 2007 an alert was disseminated by the US Food and Drug Administration (FDA) on a risk of torsades de pointes and QT prolongation, that could lead to sudden unexplained death (Beach *et al.* 2013), in patients receiving haloperidol, especially when the drug was administered intravenously or in doses higher than recommended (Meyer-Massetti *et al.* 2010). Soon after the release of this alert, several national medicines agencies recommended ECG

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monitoring before and during treatment with haloperidol, and suggested similar vigilance when prescribing other antipsychotic (AP) drugs (Meyer-Massetti *et al.* 2010). In August 2011, the FDA announced that the antidepressant (AD) citalopram had been associated with QT prolongation at high doses, informing clinicians that 'citalopram causes dose-dependent QT interval prolongation', on the basis of the results of a study undertaken in healthy volunteers given daily doses of 20 and 60 mg citalopram (Nose & Barbui, 2014). In Europe, the European Medicines Agency issued a similar warning on citalopram first, and on the antidepressant escitalopram thereafter (Nose & Barbui, 2014). In 2012 the FDA pointed out that although citalopram use should be avoided in patients with certain conditions because of the risk of QT prolongation, ECG monitoring should be performed if citalopram is used in such patients (Nose & Barbui, 2014).

As a consequence of these warnings, monitoring of the QT interval corrected for heart rate (QTc) has become increasingly common, although the possibility of identifying a pathological QTc value depends on the considered cut-off, which is not clearly defined, and on gender, as women are expected to have higher values. Under everyday circumstances, therefore, the increased risk of QTc prolongation associated with psychotropic drug exposure might be counterbalanced by increased awareness and routine ECG monitoring.

This study was therefore conducted to measure the frequency of QTc prolongation in unselected psychiatric patients, and to document the associated factors using a cross-sectional approach.

Methods

Participants

The study was carried out in 35 Italian psychiatric services that are part of the STAR (*Servizi Territoriali Associati per la Ricerca*) Network, a research group established to produce scientific knowledge by collecting data under ordinary circumstances of clinical practice. In Italy psychiatric services typically include acute inpatient wards and networks of community outpatient facilities, providing mental health care to all residents in a well-defined catchment area (Conti *et al.* 2012). During a 3-month recruitment period, a consecutive unselected series of both in- and outpatients were invited to participate. Inpatients aged 18 or above were included if they gave informed written consent, performed an ECG during hospital stay, and were receiving pharmacological treatment with psychotropic drugs on the day of ECG recording. For inpatients with more than one ECG during hospital stay, the first was considered. Outpatients aged 18 or above were included if they gave informed written consent, underwent ECG examination during the recruitment period, and were receiving pharmacological treatment with psychotropic drugs on the day of ECG performance. For outpatients with more than one ECG during the recruitment period, the first was considered. A specific psychiatric diagnosis was not a requirement for inclusion in the study. The study received ethical approval in each participating site, and all participants gave their informed written consent.

Data collection and management

Sociodemographic and clinical characteristics were collected from medical records, including ICD-10 psychiatric diagnosis, alcohol/substance use, recruitment setting, being admitted for drug overdose, heart rate, blood pressure, cardiovascular disorders, cardiovascular and psychotropic drug treatment, with information on dose regimens. Psychotropic drugs were classified following the Anatomical Therapeutic Chemical Classification (ATC) system. Antidepressants were defined as medicines in the N06A ATC group; antipsychotics in the N05A ATC group (excluding N05AN, lithium); and mood stabilisers in the N03AF, N03AG, N03AX and N05AN ATC groups. The QTc interval estimation was obtained automatically in each participating site from standard 12-lead ECG. The most common way for interpreting QTc is to divide its value by the square root of the RR interval expressed in seconds, namely, using Bazett's formula for correction. The QTc was determined by examining lead II with automatic data acquisition and was confirmed by a cardiologist who was blind to the patient's clinical condition. For descriptive purposes, based on current recommendations, the following thresholds of QTc lengthening were calculated: QTc > 450 ms; QTc > 460 ms; QTc > 480 ms; QTc > 500 ms (Taylor, 2003; Vieweg *et al.* 2012). However, considering that in men and women no accepted threshold for QTc lengthening has been established, and that the cut-off in women and men is different, in multivariate analyses QTc was considered as a continuous variable.

Psychotropic drug doses were converted into multiples of the defined daily dose (DDD) for each drug by dividing the prescribed daily dose (PDD) by the DDD (PDD/DDD) (Nose & Barbui, 2008). The DDD is the international unit of drug utilisation approved by the World Health Organisation for drug use studies. It is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its main indication in adults. Expression of drug use in terms of multiples of DDDs allows calculating, for each patient, a cumulative measure of drug consumption taking into account the concurrent

use of more than one agent. A PDD/DDD ratio of one indicates that the dose prescribed is equal to the DDD of that drug; a ratio greater than one indicates a dosage higher than the DDD of that drug, while a ratio lower than one means a dose lower than the DDD of that drug (Nose *et al.* 2008).

Data analysis

We first tested QTc as a continuous measure for evidence of association with socio-demographic information, clinical data and drug use. Spearman's rank correlation coefficients were calculated for pairs of continuous variables, and Mann–Whitney statistics were used to analyse QTc as a continuous measure by dichotomous variables.

In the whole sample of participants exposed to psychotropic drugs (model 1), linear regression analysis was run to assess the association between QTc interval and the following independent variables: sex (female = 1, male = 0), age (years, continuous variable), psychosis or related disorder (no = 0, yes = 1), length of illness (years, continuous variable), heart rate (beats per minute (bpm), continuous variable), alcohol or substance use (no = 0, yes = 1), cardiovascular disease (no = 0, yes = 1), cardiovascular drug treatment (no = 0, yes = 1), drug overdose (no = 0, yes = 1), inpatients (no = 0, yes = 1), treatment with AP only (no = 0, yes = 1), treatment with AD only (no = 0, yes = 1), and treatment with AP and AD (no = 0, yes = 1).

In the sample of participants exposed to AP drugs (model 2), linear regression analyses were run to assess the association between QTc interval and each of the following drug treatment factors: two or more AP drugs (no = 0, yes = 1), AP dose (PDD/DDD, continuous variable), second-generation AP drugs (no = 0, yes = 1), haloperidol (no = 0, yes = 1), haloperidol dose (PDD/DDD, continuous variable), risperidone (no = 0, yes = 1), clozapine (no = 0, yes = 1), olanzapine (no = 0, yes = 1), quetiapine (no = 0, yes = 1), ziprasidone (no = 0, yes = 1), paliperidone, (no = 0, yes = 1), aripiprazole (no = 0, yes = 1), asenapine (no = 0, yes = 1), any AD use in addition to AP drugs (no = 0, yes = 1), selective serotonin reuptake inhibitors (SSRI) use in addition to AP drugs (no = 0, yes = 1), citalopram in addition to AP drugs (no = 0, yes = 1), escitalopram in addition to AP drugs (no = 0, yes = 1), methadone in addition to AP drugs (no = 0, yes = 1). In order to adjust for potential confounding effects of sociodemographic and clinical variables, each of the above-reported drug-treatment factors was analysed together with the covariates from model 1.

Finally, in the sample of participants exposed to AD drugs (model 3), linear regression analyses were run to assess the association between QTc interval and the following drug treatment factors: two or more AD drugs (no = 0, yes = 1), AD dose (PDD/DDD, continuous variable), SSRI use (no = 0, yes = 1), citalopram (no = 0, yes = 1), citalopram dose (PDD/DDD, continuous variable), escitalopram (no = 0, yes = 1), escitalopram dose (PDD/DDD, continuous variable), methadone (no = 0, yes = 1), any AP use in addition to AD drugs (no = 0, yes = 1), second-generation AP in addition to AD drugs (no = 0, yes = 1), haloperidol in addition to AD drugs (no = 0, yes = 1), risperidone in addition to AD drugs (no = 0, yes = 1), clozapine in addition to AD drugs (no = 0, yes = 1), olanzapine in addition to AD drugs (no = 0, yes = 1), quetiapine in addition to AD drugs (no = 0, yes = 1), ziprasidone in addition to AD drugs (no = 0, yes = 1), paliperidone in addition to AD drugs (no = 0, yes = 1), aripiprazole in addition to AD drugs (no = 0, yes = 1) and asenapine in addition to AD drugs (no = 0, yes = 1). In order to adjust for potential confounding effects of sociodemographic and clinical variables, each of the above-reported drug-treatment factors was analysed together with the covariates from model 1.

A non-parametric bootstrap method of statistical accuracy was used, assuming that the observed distribution of the present sample was a good estimate of the true population distribution (Efron B & Tibshirani R, 1986).

Results

Patient characteristics

During the recruitment period a total of 2411 patients were identified, agreed to participate and were included in the study. No patients refused to participate. The main sociodemographic and clinical characteristics are presented in Table 1. The mean age was approximately 50 years, with an equal distribution between men and women; on average, length of illness was 12 years, and more than one-third had a diagnosis of psychotic disorder. More than two-thirds were recruited as inpatients. The majority was receiving treatment with AP drugs, less than half with AD drugs. On the average, both AP and AD drugs were given at doses very close to the DDD (Table 1).

Prevalence of QTc prolongation

Table 2 reports the prevalence of QTc prolongation in men and women. According to the threshold used, it ranged from slightly less than 20% for the cut-off of 450 milliseconds (ms) to around 1% for the cut-off of 500 ms. As expected, the prevalence was higher in women.

Factors associated with QTc prolongation – univariate analyses

The relationship between the sociodemographic and clinical variables reported in Table 1 and QTc

Table 1. *Demographic and clinical characteristics of patients exposed to psychotropic drugs* ($N = 2411$)

Variable	Value *N* (%)/mean (S.D.)	Univariate association with QTc (*p* value)
Female sex	1287 (53.7)	<0.001
Mean (S.D.) age (years)	48.9 (30.2)	<0.001
Psychosis or related disorder	867 (35.5)	0.459
Mean (S.D.) length of illness (years)	12.2 (11.9)	<0.001
Mean (S.D.) heart rate (bpm)	79.1 (15.3)	<0.001
Alcohol or substance use	452 (18.7)	0.082
Cardiovascular disease	661 (29.8)	<0.001
Drug overdose	212 (9.21)	<0.001
Inpatients	1873 (77.6)	<0.001
Treatment with AP	1783 (73.9)	0.126
Treatment with AD	1005 (41.6)	0.017
Treatment with AP only	1204 (49.9)	0.003
Treatment with AD only	426 (17.6)	0.305
Treatment with AP and AD	579 (24.0)	0.068
Mean AP dose (PDD/DDD)	1.11 (1.02)	<0.001
Mean AD dose (PDD/DDD)	1.61 (1.27)	0.466

AP, antipsychotic drugs; AD, antidepressant drugs; PDD, prescribed daily dose; DDD, defined daily dose.

prolongation was initially tested in univariate association analyses. As reported in Table 1, female sex, age, length of illness, heart rate, cardiovascular diseases, drug overdose, inpatients status, treatment with AD, treatment with AP only and AP dose, were all significantly associated with QTc prolongation.

Factors associated with QTc prolongation – multivariate analyses

In the first multivariate model conducted in the whole sample of patients exposed to psychotropic drugs (Table 3), female sex, age, heart rate, alcohol and/or substance abuse, cardiovascular diseases and cardiovascular drug treatment, drug overdose and being inpatients were significantly associated with QTc prolongation (model 1).

After adjustment for the variables included in model 1, we investigated drug treatment factors associated with QTc prolongation (Table 4) in the sample of patients exposed to AP drugs (model 2). Use of two or more AP drugs was positively associated with QTc prolongation, while use of aripiprazole decreased the risk. Use of haloperidol, as well as use of citalopram or escitalopram in addition to AP drugs, was not associated with QTc prolongation.

Similarly, after adjustment for the variables included in model 1, we investigated drug treatment factors associated with QTc prolongation (Table 5) in the sample of patients exposed to AD drugs (model 3). Use of citalopram, and citalopram dose, were positively associated with QTc prolongation, as was the case of use of haloperidol in addition to AD drugs.

Discussion

In a large unselected sample of ordinary practice in- and out-patients, the prevalence of individuals with

Table 2. *Prevalence of QTc prolongation in patients exposed to psychotropic drugs* ($n = 2411$)

	MEN ($n = 1124$)		WOMEN ($n = 1287$)	
QTc prolongation threshold (ms)	*N*	% (95% CI)	*N*	% (95% CI)
450–459	163	14.7 (12.6–16.9)	239	18.6 (16.4–20.8)
460–479	86	7.75 (6.24–9.48)	124	9.63 (8.07–11.3)
480–499	37	3.34 (2.35–4.56)	44	3.42 (2.49–4.56)
>500	14	1.26 (0.69–2.10)	13	1.01 (0.53–1.72)

ms, milliseconds; CI, confidence interval.

Table 3. *Factors associated with QTc prolongation in patients exposed to psychotropic drugs* (*model* 1)*: linear regression analysis* (*bootstrapped* 95% *CIs*)

Explanatory variable	Coefficient (bias corrected 95% CI)	*z* value	*p* value
Sex (male = 0, female = 1)	8.88 (6.38–11.39)	6.96	<0.001
Age > 65 years (no = 0, yes = 1)	5.27 (0.97–9.57)	2.40	0.016
Psychosis or related disorder (no = 0, yes = 1)	2.92 (−0.65–6.50)	1.60	0.109
Length of illness (years)	0.01 (−0.01–0.01)	0.20	0.838
Heart rate (bpm, continuous variable)	0.59 (0.51–0.67)	14.08	<0.001
Alcohol or substance use (no = 0, yes = 1)	3.87 (1.57–6.17)	3.31	0.001
Cardiovascular disease (no = 0, yes = 1)	13.66 (11.27–16.04)	11.23	<0.001
Cardiovascular drug treatment (no = 0, yes = 1)	4.07 (0.63–7.52)	2.32	0.020
Drug overdose (no = 0, yes = 1)	7.91 (3.04–12.79)	3.19	0.001
Inpatients (no = 0, yes = 1)	10.52 (7.17–13.88)	6.15	<0.001
Treatment with AP only (no = 0, yes = 1)	1.22 (−3.86–6.31)	0.47	0.638
Treatment with AD only (no = 0, yes = 1)	3.15 (−2.36–8.68)	1.12	0.262
Treatment with AP and AD (no = 0, yes = 1)	0.12 (−5.28–5.53)	0.05	0.964
Constant term	342.78 (333.74–351.82)	74.32	<0.001

CI, confidence interval; bpm, beats per minute; AP, antipsychotic drugs; AD, antidepressant drugs.

a QTc above 500 ms was around 1%, while slightly more than 3% had a QTc above 480 ms. These findings are in agreement with recent data collected in adult psychiatric inpatients by Girardin *et al.*, who found that among 6790 psychiatric inpatients 0.9% qualified as long QT case subjects (QTc > 500 ms) (Girardin *et al.* 2013). Other previous surveys reported prevalence rates between 1.2 and 2.6% (Sadanaga *et al.* 2004; Ramos-Rios *et al.* 2010; Pasquier *et al.* 2012).

Strengths of this pharmacoepidemiological survey include recruitment of ordinary practice patients employing very wide entry criteria with almost no exclusion criteria, and the multicentre approach which most likely increased generalisability of study

Table 4. *Drug treatment factors associated with QTc prolongation in patients exposed to antipsychotic drugs* (*model* 2)*: linear regression analysis* (*bootstrapped* 95% *CIs*)

Explanatory variable	Coefficient* (bias corrected 95% CI)	*z* value	*p* value
Two or more AP drugs (no = 0, yes = 1)	3.62 (1.08–6.16)	2.79	0.005
AP dose (PDD/DDD, continuous variable)	1.39 (−0.40–3.18)	1.52	0.130
Second-generation AP drugs (no = 0, yes = 1)	1.25 (−1.64–4.14)	0.85	0.398
Haloperidol (no = 0, yes = 1)	0.69 (−3.32–4.72)	0.34	0.734
Haloperidol dose (PDD/DDD, continuous variable)	−0.44 (−2.85–1.96)	−0.36	0.719
Risperidone (no = 0, yes = 1)	−2.39 (−6.70–1.91)	−1.09	0.275
Clozapine (no = 0, yes = 1)	3.39 (−2.46–9.26)	1.14	0.256
Olanzapine (no = 0, yes = 1)	−0.21 (−3.36–2.93)	−0.13	0.895
Quetiapine (no = 0, yes = 1)	2.50 (−1.03–6.05)	1.39	0.165
Ziprasidone (no = 0, yes = 1)	−2.29 (−29.52–24.92)	−0.17	0.869
Paliperidone (no = 0, yes = 1)	−3.83 (−12.69–5.01)	−0.85	0.396
Aripiprazole (no = 0, yes = 1)	−7.11 (−13.47–0.74)	−2.19	0.029
Asenapine (no = 0, yes = 1)	−5.03 (−15.31–5.24)	−0.96	0.337
Any AD use in addition to AP drugs (no = 0, yes = 1)	−0.81 (−5.40–3.77)	−0.35	0.728
SSRI use in addition to AP drugs (no = 0, yes = 1)	1.21 (−2.53–4.95)	0.63	0.526
Citalopram in addition to AP drugs (no = 0, yes = 1)	5.92 (−3.08–14.94)	1.29	0.198
Escitalopram in addition to AP drugs (no = 0, yes = 1)	4.52 (−2.43–11.48)	1.28	0.202
Methadone in addition to AP drugs (no = 0, yes = 1)	−0.92 (−14.49–12.64)	−0.13	0.894

CI, confidence interval; AP, antipsychotic drugs; AD, antidepressant drugs; SSRI, selective serotonin-reuptake inhibitors.
*Adjusted for the following variables: sex, age, psychosis or related disorder, heart rate, alcohol or substance use, cardiovascular disease, cardiovascular drug treatment, drug overdose, inpatients.

Table 5. *Drug treatment factors associated with QTc prolongation in patients exposed to antidepressant drugs* (*model* 3)*: linear regression analysis* (*bootstrapped* 95% *CIs*)

Explanatory variable	Coefficient* (bias corrected 95% CI)	*z* value	*p* value
Two or more AD drugs (no = 0, yes = 1)	−1.73 (−8.70–5.22)	−0.49	0.625
AD dose (PDD/DDD, continuous variable)	0.02 (−1.95–2.00)	0.02	0.983
SSRIs (no = 0, yes = 1)	2.16 (−1.76–6.08)	1.08	0.280
Citalopram (no = 0, yes = 1)	5.77 (0.31–11.23)	2.07	**0.038**
Citalopram dose (PDD/DDD, continuous variable)	3.44 (0.71–6.16)	2.48	**0.013**
Escitalopram (no = 0, yes = 1)	2.21 (−3.74–8.17)	0.73	0.467
Escitalopram dose (PDD/DDD, continuous variable)	3.36 (−1.21–7.94)	1.44	0.150
Methadone (no = 0, yes = 1)	4.68 (−18.62–27.99)	0.39	0.694
Any AP use in addition to AD drugs (no = 0, yes = 1)	3.20 (−2.54–8.95)	1.09	0.274
Second-generation APs in addition to AD drugs (no = 0, yes = 1)	−1.69 (−6.52–3.14)	−0.69	0.492
Haloperidol in addition to AD drugs (no = 0, yes = 1)	9.23 (0.56–17.90)	2.09	**0.037**
Risperidone in addition to AD drugs (no = 0, yes = 1)	−7.59 (−18.46–3.26)	−1.37	0.171
Clozapine in addition to AD drugs (no = 0, yes = 1)	1.99 (−17.99–21.98)	0.20	0.845
Olanzapine in addition to AD drugs (no = 0, yes = 1)	0.52 (−7.29–8.34)	0.13	0.895
Quetiapine in addition to AD drugs (no = 0, yes = 1)	−1.78 (−6.74–3.16)	−0.71	0.479
Ziprasidone in addition to AD drugs (no = 0, yes = 1)	8.87 (−23.73–41.48)	0.53	0.594
Paliperidone in addition to AD drugs (no = 0, yes = 1)	−5.10 (−39.89–29.69)	−0.29	0.774
Aripiprazole in addition to AD drugs (no = 0, yes = 1)	−10.22 (−22.92–2.46)	−1.58	0.114
Asenapine in addition to AD drugs (no = 0, yes = 1)	−9.70 (−28.55–9.13)	−1.01	0.313

CI, confidence interval; AP, antipsychotic drugs; AD, antidepressant drugs; SSRI, selective serotonin-reuptake inhibitors.
*Adjusted for the following variables: sex, age, psychosis or related disorder, heart rate, alcohol or substance use, cardiovascular disease, cardiovascular drug treatment, drug overdose, inpatients.

findings. The identification of female sex, older age, increased heart rate, alcohol and/or substance use disorders and cardiovascular disorders as correlates of prolonged QTc further corroborates generalisability of study findings, as these are variables known to be associated with ECG abnormalities, including prolonged QTc (Beach *et al.* 2013).

However, there are limitations that should be considered. First, the cross-sectional design that was employed does not allow generating information about the temporal relationship between drug exposure and QTc prolongation, and therefore no causality assessment can be undertaken. Second, no outcome data were collected, which means that the clinical relevance of QTc prolongation, in terms of probability of torsade de pointes and sudden death, was not assessed. In the study carried out by Girardin *et al.*, for example, it was possible to establish that sudden cardiac death was recorded in five patients, and torsade de pointes in seven other patients (Girardin *et al.* 2013). Although a cut-off at 500 ms is usually accepted as indicative of a high risk for arrhythmic events, the lack of outcome data leaves uncertainty on which QTc threshold is clinically meaningful in terms of risk of ECG abnormalities. We consequently employed different thresholds for descriptive purposes, and QTc values were used as continuous variable in multivariate analyses. Third, the small numbers of patients taking some individual drugs resulted in limited statistical power to detect their possible associations with QTc prolongation, as reflected by wide confidence intervals. Fourth, we did not enrol a control group of individuals who were not receiving psychotropic drugs. Although this would have been useful to have a risk in a comparison population, we argued that in- and out-patients who do not receive any drug treatment would have been too different from our population to act as a reliable comparison group. Last, the choice of using ECG data collected for clinical purposes, which may have introduced some heterogeneity in terms of different centres measuring the QT interval in slightly different ways, was motivated by an attempt to resemble clinical practice as much as possible.

Overall, the relatively low prevalence of QTc prolongation may be interpreted in two different directions. One possibility is that the true risk of ECG abnormalities associated with psychotropic drugs has been over estimated. For example, the citalopram study that prompted safety warnings by regulatory authorities did not measure the proportion of subjects with QTc above a certain threshold, but only reported a mean change from baseline to follow-up in QTc of 7.5 ms with citalopram 20 mg/day and 16.7 ms with

citalopram 60 mg/day. Similarly, for escitalopram the change from baseline in QTc was 4.3 ms with 10 mg/day and 10.7 ms with 30 mg/day. Clearly, the clinical relevance of increases of 10–15 ms is questionable, and may also have different meanings depending on baseline values. For antipsychotics, including haloperidol, most data suggested a dose-dependent risk increase, with low doses associated with almost no increase (Reilly *et al.* 2000; Hasnain & Vieweg, 2014). Considering that in our sample of ordinary practice patients AP doses were on average very close to the DDD of each agent, very little impact on QTc values may be expected.

A second possible interpretation is that the relatively low prevalence of QTc prolongation may be the result of safety warnings. Safety warnings have indubitably increased attention on ECG abnormalities in individuals treated with psychotropic drugs, and therefore those who receive treatment might be those who have been selected for having no ECG abnormalities. In other clinical populations prevalence rates are much higher. In medical inpatients, for example, the prevalence of QTc prolongation may be as high as 22% (Pasquier *et al.* 2012), whereas in surgical patients QTc prolongation was shown to affect 6% of a sample of elderly surgical patients (van Haelst *et al.* 2014). It is also interesting to note that the safety warning for haloperidol, issued in 2007, might have been better integrated into routine clinical practice in comparison with that on citalopram and escitalopram, which was issued more recently, in 2011. This might explain the finding that while use of haloperidol, and haloperidol dose, was not associated with QTc prolongation (which may be the result of careful ECG monitoring before drug use), use of citalopram, and citalopram dose, was found to be significantly associated with QTc prolongation.

In terms of AP-related factors, use of two or more AP drugs significantly increased the risk. This is a very relevant finding as the number of AP drugs is a proxy of total AP dose, which is an established risk factor of QTc prolongation (Sala *et al.* 2005). Another interesting finding on AP drugs refers to aripiprazole, which resulted, in comparison with all other AP drugs, associated with a reduced risk of QTc prolongation. This epidemiological finding is highly consistent with experimental data from placebo and head-to-head comparisons between different AP drugs, recently reviewed by Leucht *et al.* (2013). They found that aripiprazole was not associated with significant QTc prolongation compared with placebo, and that it was the second best choice in terms of risk of ECG abnormalities after lurasidone (not licensed in Italy).

In terms of AD-related factors, we could detect noteworthy differences for citalopram but not for escitalopram. This is unlikely to be a reflection of different safety warning modalities, which were very similar, and should not reflect a power problem, as can be inferred by the confidence intervals around the coefficient estimates. However, it might be possible that the two AD drugs actually bear a different risk of QTc prolongation. This possibility has recently been suggested by Beach *et al.*, who carried out a systematic review of prospective studies investigating the association between SSRI use and QTc values. The review found that the association between citalopram and QTc prolongation was stronger than for most other SSRIs (Beach *et al.* 2014). Castro *et al.*, by contrast, who carried out an analysis of electronic health records, suggested a modest QTc prolongation for both citalopram and escitalopram (Castro *et al.* 2013).

The confirmation of a link between AP polypharmacy and QTc prolongation supports current guidelines that recommend avoiding the concurrent use of two or more AP drugs, and the confirmation of a link between citalopram and QTc prolongation supports the need for routine QTc monitoring. The relatively low proportion of patients with QTc prolongation suggests compliance with current safety warnings issued by regulatory authorities, but also casts some doubts on the clinical relevance of QTc prolongation related to psychotropic drugs. What still remains to be formally assessed is the cost-utility of such monitoring programmes.

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Conflict of Interest

None.

Ethical Standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Appendix 1

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