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Antipsychotics in routine treatment are minor contributors to QT prolongation compared to genetics and age

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Abstract

Background: Drug-induced prolongation of cardiac repolarization limits the treatment with many psychotropic drugs. Recently, the contribution of polygenic variation to the individual duration of the QT interval was identified.

Aims: To explore the interaction between antipsychotic drugs and the individual polygenic influence on the QT interval.

Methods: Retrospective analysis of clinical and genotype data of 804 psychiatric inpatients diagnosed with a psychotic disorder. The individual polygenic influence on the QT interval was calculated according to the method of Arking et al.

Results: Linear regression modelling showed a significant association of the individual polygenic QT interval score ($\beta_{std} = 0.176$, $p < 0.001$) and age ($\beta_{std} = 0.139$, $p < 0.001$) with the QTc interval corrected according to Fridericia's formula. Sex showed a nominal trend towards significance ($\beta_{std} = 0.064$, $p = 0.064$). No association was observed for the number of QT prolonging drugs according to AZCERT taken. Subsample analysis ($n = 588$) showed a significant association of potassium serum concentrations with the QTc interval ($\beta_{std} = -0.104$, $p = 0.010$). Haloperidol serum concentrations were associated with the QTc interval only in single medication analysis ($n = 26$, $\beta_{std} = 0.101$, $p = 0.004$), but not in multivariate regression analysis. No association was observed for aripiprazole, clozapine, quetiapine and perazine, while olanzapine and the sum of risperidone and its metabolite showed a negative association.

Conclusions: Individual genetic factors and age are main determinants of the QT interval. Antipsychotic drug serum concentrations within the therapeutic range contribute to QTc prolongation on an individual level.

Keywords

QT prolongation, polygenic score, antipsychotic medication, psychotic disorder

Introduction

Drug-induced dysregulation of cardiac repolarization leading to prolongation of the QTc interval is an important risk factor for the development of *torsade de pointes* (TdP) tachyarrhythmia and sudden cardiac death (Roden, 2004). Psychopharmacological drugs prolong the QT interval, rendering drug-induced sudden cardiac death to be a key issue for the safety of psychopharmacological treatment (Beach et al., 2013, 2018; Wenzel-Seifert et al., 2011). On the molecular level, drug-induced prolongation of the QT interval involves mechanisms resembling those of congenital long QT syndromes, most notably inhibition of ion channel conductance such as the delayed rectifying hERG (*KCNQ2*) potassium channel, but also other proteins such as the nitric oxide synthase 1 adaptor protein (*NOS1AP*) (Kannankeril et al., 2010; Napolitano et al., 2015; Sanguinetti and Tristani-Firouzi, 2006). The affinity of psychotropic drugs towards cardiac ion channels is lower than their affinity towards their primary pharmacological targets such as the dopamine D₂- or the serotonin 5-HT_{2A}-receptor and the K_d of ion channel inhibition is above the therapeutic range (Abi-Gerges et al., 2011; Hiemke et al., 2018; Silvestre et al., 2014). Nevertheless, due to accumulation of drugs in cardiac tissues leading to locally toxic concentrations or

accidental intoxication, QT prolongation is feasible even under therapeutic drug concentrations (Mikkelsen et al., 2018). However, clinical studies on this topic showed inconsistent results. An association of QTc prolongation was observed for antipsychotic polypharmacy when correcting the QT interval using Bazett's formula, but not when using Fridericia's formula, thereby possibly pointing at the limitations of different QTc correction formulas (Barbui et al., 2016; Elliott et al., 2018; Nosé

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et al., 2016). Recently, common genetic variants were identified to exhibit a strong additive effect on the duration of the individual QT interval (Arking et al., 2014; Newton-Cheh et al., 2009; Pfeufer et al., 2005). Since the effects of drugs and genetics are supposed to be additive, drug-induced QTc prolongation may act as a second hit on genetically predisposed individuals leading to sudden cardiac death (Roden, 2008; Strauss et al., 2017). Therefore, we hypothesized that individual genetic factors may explain an individual prolongation of the QT interval upon administration of antipsychotic drugs with serum concentrations within the therapeutic range.

Material and methods

Patient sample and genotyping

Genotype data generated with Illumina PsychArray BeadChip as part of the Psychiatric Genomics Consortium initiative (PGC) and approved by the Ethics Committee of the University of Würzburg [72/99; 184/11] in accordance with the Declaration of Helsinki, was available for 2062 inpatients of the Department of Psychiatry and Psychotherapy at the University Hospital (Clinic) of Würzburg diagnosed with a psychotic disorder according to the criteria of DSM-5. All subjects were unrelated and of German Caucasian descent. Written informed consent was obtained from all patients. This sample was retrospectively screened for routine clinical data in accordance with the local ethics committee. Patients were considered for further analysis when drugs had been administered in steady state (applied without change for at least four consecutive half-lives) and coincident electrocardiography was available. Patients were excluded with signs of or a previously documented atrial fibrillation, QRS duration greater than 120 ms, bundle branch block, intraventricular conduction delay, electronic pacemaker, congestive heart failure and dilated cardiomyopathy, in line with the exclusion criteria used by the GWAS analysis by Arking and coworkers (Arking et al., 2014) or lithium levels above 0.8 mmol/L were excluded. Taken together, 804 patients were analysed based on these criteria.

Single nucleotide polymorphism (SNP) selection and calculation of the score for the individual polygenic influence on the duration of the QT interval

Polygenic scores for the individual polygenic influence on the duration of the QT interval were calculated in the imputed target sample based on the summary statistics of the genome-wide association study by Arking and coworkers (Arking et al., 2014). Regarding our sample, only SNPs with an INFO imputation quality score > 0.6 and a minor allele frequency > 0.01 and < 0.99 were used for calculation. Strand ambiguous SNPs were removed, leaving 3,597,705 overlapping SNPs between the discovery and the target sample. We performed p -value-informed clumping with a cut-off $r^2 = 0.1$ using a 500-kb window (index variant p -value threshold = 1, clumped variant p -value threshold = 1) according to the European subsample of the 1000 Genomes Project phase 1 as a reference (1000 Genomes Project Consortium et al., 2012). The number of effect alleles for each variant below a given threshold of the p -value ($p < 5 \times 10^{-8}$, $p < 1 \times 10^{-6}$,

$p < 1 \times 10^{-4}$, $p < 0.001$, $p < 0.01$, $p < 0.05$, $p < 0.1$, $p < 0.2$, $p < 0.5$, $p < 1$) was multiplied by the effect estimates in milliseconds of the discovery sample. The sum of per allele scores across an individual represents the individual polygenic influence on the QT interval. If not indicated otherwise, the calculated score used included variants with a p -value below 5×10^{-8} , corresponding to previous analyses (Noseworthy et al., 2011; Strauss et al., 2017). The genetic population structure inference of the sample was taken into account in all calculated models using principal component analysis (Price et al., 2006).

Electrocardiography

Electrocardiography was performed with a Cardiofax ECG-1350 (Nihon Kohden, Rosbach, Germany) by a 12-lead recording and automated analysis of the heart rate and uncorrected QT interval. The validity of the measurement was verified by a trained physician and inconsistent measurements were excluded from further analysis. The QT interval depends on the heart rate and several methods have been developed to perform a reliable frequency adaption. Recent genetic studies on the QT interval have adopted using Fridericia's formula, which corrects the QTc interval using the cubic root of the RR interval for a wide range of heart rates contrary to Bazett's formula using the square root of the RR interval (Arking et al., 2014; Newton-Cheh et al., 2009; Pfeufer et al., 2005). We adhered to the correction using Fridericia's formula in our study.

Drug serum concentration measurement

Drug serum concentration measurement was performed on a routine basis during treatment in a naturalistic setting. Trough-level measurement was conducted under steady state conditions upon applying the last dose for at least four elimination half-lives. Drug concentration was determined by isocratic liquid chromatography (HPLC) with reversed phase columns and photometric detection as previously published (Scherf-Clavel et al., 2019). Analysis was carried out in the Laboratory for Therapeutic Drug Monitoring of the Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg. Internal and external quality control programs by Cardiff Bioanalytical Services (The Cardiff Medical Center, Cardiff, UK, prior to 2011) and Instand e.V. (Düsseldorf, Germany, from 2011 to present) were operated regularly without rejection.

Statistical analysis

Statistical analysis using descriptive statistics, multiple linear regression modelling and ANOVA as indicated in the text was performed using SPSS version 26.0 (IBM, Armonk, USA). A p -value < 0.05 was considered to be statistically significant if not indicated otherwise. Regression models calculated using polygenic scores were corrected for genetic population structure inference by including the first and second component of the principal component analysis of the genotype data of the complete patient sample. The number of QT prolonging drugs each patient received was calculated referring to drugs listed with known, potential and conditional risk according to AZCERT (www.crediblemeds.org, Oro Valley, USA) retrieved on 15 January 2021 (Schwartz and Woosley, 2016).

Table 1. Demographics and clinical data of all patients ($n = 804$). QTcF represents the QT interval corrected according to Fridericia's formula. PRS is the polygenic risk score for the individual polygenic influence on the duration of the QTc interval. The number of QT-prolonging drugs according to AZCERT taken simultaneously is reported.

	Mean \pm SD	Range
Age (years)	39.8 \pm 11.7	18.1–72.0
Sex (female:male)	284:520	
QTcF	406.1 \pm 19.5	343–570
PRS (ms)	4.54 \pm 3.52	–6.32–14.30
QT prolonging drugs (n)	2.22 \pm 1.24	0–7
Antipsychotic drugs (n)	1.48 \pm 0.88	0–5
1st-gen. antipsychotic drugs (n)	0.65 \pm 0.73	0–3
2nd-gen. antipsychotic drugs (n)	0.79 \pm 0.70	0–3

Results

Eight hundred and four patients were included into analysis (Table 1). Following previous analyses, a score for the individual polygenic influence on the QT interval was calculated using a cut-off of $p < 5 \times 10^{-8}$ on a genome wide level, including 71 single nucleotide polymorphisms (Arking et al., 2014; Strauss et al., 2017). QT prolonging drugs administered in the sample and considered in the analyses were selected according to AZCERT and are presented in Table 2.

Linear regression modelling of the heart-rate corrected QTc interval according to Fridericia's formula was conducted for an increasing number of predictors as shown in Table 3. Across all models, the individual polygenic QT interval score showed a significant association with a robust effect size with the heart-rate corrected QTc interval according to Fridericia's formula in line with previous reports (Arking et al., 2014; Strauss et al., 2017). Taking additionally age, sex and the number of QT-prolonging drugs applied into account revealed a significant effect for each pair of predictors. However, upon inclusion of all predictors, a significant effect was observed for the individual polygenic QT interval score ($\beta_{\text{std}} = 0.176, p < 0.001$) and age ($\beta_{\text{std}} = 0.139, p < 0.001$) only. Sex showed a nominal trend towards significance, but the number of QT-prolonging drugs did not. In the subsample with electrolyte measurements, the QTc interval showed a significant association with decreasing potassium concentrations as expected ($n = 588, \beta_{\text{std}} = -0.104, p = 0.010$). In order to investigate a link between antipsychotic drugs and subsequent prolongation of the QT interval, the relationship between drug serum concentrations of antipsychotic drugs and the QTc interval was analysed (Table 4). In single medication analysis, increasing concentrations of haloperidol ($n = 26, \beta_{\text{std}} = 0.101, p = 0.004$) and decreasing concentrations of olanzapine ($n = 17, \beta_{\text{std}} = -0.079, p = 0.025$) showed a nominal significant association with the QTc interval. No association was observed for aripiprazole, clozapine, perazine and quetiapine. In multivariate regression modelling of the QTc interval taking the individual polygenic QT interval score, age, sex, the number of QT-prolonging drugs applied and the serum level of antipsychotic drugs into account, a nominal significant negative association of the QTc interval with olanzapine serum concentrations ($n = 17, \beta_{\text{std}} = -0.076, p = 0.027$) and the sum of the concentrations of risperidone and its metabolite 9-OH-risperidone/paliperidone ($n = 72, \beta_{\text{std}} = -0.086, p = 0.014$)

was observed. These nominal associations were maintained when controlling for potassium serum concentrations.

To further analyse QTc prolongation upon antipsychotic polypharmacy, a possible link between the number of antipsychotic drugs applied and the QTc interval was investigated (Table 5). Across the complete sample, a significant association was observed between the number of first-generation antipsychotic drugs applied and the QTc interval ($\beta_{\text{std}} = 0.092, p = 0.007$). Controlling for potassium serum levels, the association remained at nominal significance with a comparable effect size ($\beta_{\text{std}} = 0.080, p = 0.046$). Subsample analysis showed that this association was mediated by participants receiving additionally second-generation antipsychotic drugs. No association was observed for the total number or the number of second-generation antipsychotic drugs applied.

Discussion

Antipsychotic drugs may delay cardiac repolarization and raise the risk for sudden cardiac death in the presence of risk factors such as spontaneous depolarization or electrolyte disbalance (Glassman and Bigger, 2001; Raschi et al., 2013; Salvo et al., 2016; Turker et al., 2017). Our results confirm the concept of a repolarization reserve and point at the strong additive polygenic effects on the individual duration of the QT interval (Strauss et al., 2017). However, the overall effect size of the genetic effect was small, in line with a previous report suggesting that the individual polygenic QT interval score and clinical variables explained about 10–15% of the variation of the QT interval (Rosenberg et al., 2017).

Our data emphasize the use of Fridericia's formula to correct the QTc interval, which applies the cubic root of the RR interval, contrary to Bazett's formula applying the square root. The problem of QTc overcorrection due to Bazett's formula becomes uncovered in patient samples receiving tachycardia inducing mediations: correction with Bazett's formula yields a highly significant association between the QTcB interval and serum levels of clozapine ($n = 103, \beta_{\text{std}} = 0.169, p < 0.001$), contrary to results using Fridericia's formula ($n = 103, \beta_{\text{std}} = 0.003, p = 0.488$). Correction of the QTc interval using Fridericia's formula was therefore also applied in recent genome-wide association studies of the QT interval in order to minimize the correction error, still acknowledging that any correction formula may introduce uncertainty on an individual level of the QTc interval (Arking et al., 2014; Isbister and Page, 2013). Taken together, the partial agreement of our results with previous studies may therefore result not only from correction of the genetic effect and different inclusion/exclusion criteria in our sample, but also from applying Fridericia's formula, since our results are generally in line with studies applying Fridericia's formula (Barbui et al., 2016; Beach et al., 2013, 2018; Elliott et al., 2018; Hasnain and Vieweg, 2014; Meid et al., 2017; Nielsen, 2012; Noordam et al., 2015; Nosè et al., 2016; Wenzel-Seifert et al., 2011). Drug-induced QT prolongation depends on the drug serum concentration. We observed a significant association of haloperidol serum concentrations with the QTc interval in single medication analysis, which retained a comparable effect size albeit only significant at nominal trend level in multivariate regression modelling. This result may be related to the

Table 2. Summary of drugs reported to prolong the QTc interval according to AZCERT. The number of study participants taking the corresponding drug as well as AZCERT risk category and pharmacological drug class according to the Neuroscience-based Nomenclature (nbn) are given (Nutt and Blier, 2016).

	Individuals (n, %)		AZCERT category	Drug class
Amisulpride	20	2.5	Conditional risk	2nd generation antipsychotic
Amitriptyline	110	13.7	Conditional risk	TCA
Aripiprazole	69	8.5	Possible risk	2nd generation antipsychotic
Benperidol	9	1.1	Possible risk	1st generation antipsychotic
Chlorprothixene	40	5.0	Known risk	1st generation antipsychotic
Citalopram	5	0.6	Known risk	SSRI
Clarithromycin	2	0.3	Known risk	Antibiotic
Clomipramine	67	8.3	Conditional risk	TCA
Clozapin	170	21.1	Possible risk	2nd generation antipsychotic
Diphenhydramine	2	0.3	Conditional risk	Antihistamine
Donepezil	2	0.3	Known risk	Cholinesterase inhibitor
Doxepin	87	10.8	Conditional risk	TCA
Escitalopram	47	5.9	Known risk	SSRI
Esomeprazole	3	0.4	Conditional risk	Proton pump inhibitor
Famotidine	1	0.1	Conditional risk	H2-receptor antagonist
Fluoxetine	2	0.3	Conditional risk	SSRI
Flupentixol	97	12.0	Possible risk	1st generation antipsychotic
Furosemide	1	0.1	Conditional risk	Diuretic
Haloperidol	144	17.8	Known risk	1st generation antipsychotic
Hydrochlorothiazide	28	3.5	Conditional risk	Diuretic
Imipramine	4	0.5	Possible risk	TCA
Levofloxacin	1	0.1	Known risk	Antibiotic
Levomepromazine	2	0.3	Known risk	1st generation antipsychotic
Lithium	111	13.7	Possible risk	Mood stabilizer
Loperamide	1	0.1	Conditional risk	Opioid agonist
Maprotiline	15	1.9	Possible risk	TeCA
Melperone	35	4.4	Possible risk	1st generation antipsychotic
Memantine	1	0.1	Possible risk	NMDA receptor antagonist
Metoclopramide	5	0.6	Conditional risk	Antiemetic
Mirtazapine	63	7.8	Possible risk	TeCA
Nortriptyline	17	2.1	Possible risk	TCA
Olanzapine	59	7.3	Conditional risk	2nd generation antipsychotic
Omeprazole	3	0.4	Conditional risk	Proton pump inhibitor
Paliperidone	9	1.1	Possible risk	2nd generation antipsychotic
Pantoprazole	75	9.3	Conditional risk	Proton pump inhibitor
Paroxetine	5	0.6	Conditional risk	SSRI
Perphenazine	7	0.9	Possible risk	1st generation antipsychotic
Pipamperone	31	3.9	Possible risk	1st generation antipsychotic
Promethazine	2	0.2	Possible risk	1st generation antipsychotic
Quetiapine	162	20.2	Conditional risk	2nd generation antipsychotic
Risperidone	145	18.0	Conditional risk	2nd generation antipsychotic
Sertraline	12	1.5	Conditional risk	SSRI
Sulpiride	1	0.1	Known risk	1st generation antipsychotic
Tamoxifen	1	0.1	Possible risk	Anti-cancer
Tiapride	2	0.3	Possible risk	D2-, D3-dopaminergic receptor antagonist
Tolterodine	1	0.1	Possible risk	M2-, M3-cholinergic receptor antagonist
Torasemide	11	1.4	Conditional risk	Diuretic
Tramadol	2	0.3	Possible risk	Opioid agonist
Trimipramine	3	0.4	Possible risk	TCA
Venlafaxine	60	7.5	Possible risk	SNRI
Ziprasidone	20	2.5	Conditional risk	2nd generation antipsychotic
Zuclopenthixol	10	1.2	Known risk	1st generation antipsychotic

SNRI: Serotonin Noradrenaline Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressant; TeCA: Tetracyclic Antidepressant.

Table 3. Linear regression modelling of the QTc interval corrected according to Fridericia's formula for an increasing number of predictors. Positive β of sex indicates increasing risk in female patients. A p -value < 0.05 was considered statistically significant; model 1–5: $n = 804$, model 6: $n = 588$.

	Model 1			Model 2			Model 3		
	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p
Genetic QT score (ms)	0.97 ± 0.19	0.175	< 0.001	1.01 ± 0.19	0.183	< 0.001	0.93 ± 0.19	0.168	< 0.001
Age (years)				0.27 ± 0.06	0.163	< 0.001			
Sex							3.56 ± 1.42	0.087	0.012
	Model 4			Model 5			Model 6		
	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p
Genetic QT score (ms)	0.97 ± 0.23	0.175	< 0.001	0.98 ± 0.19	0.176	< 0.001	1.03 ± 0.23	0.184	< 0.001
Age (years)				0.23 ± 0.06	0.139	< 0.001	0.29 ± 0.07	0.176	< 0.001
Sex				2.63 ± 1.42	0.064	0.064	2.76 ± 1.73	0.065	0.111
QT prolonging drugs (n)	1.43 ± 0.55	0.09	0.009	0.89 ± 0.56	0.056	0.111	0.48 ± 0.68	0.03	0.476
Serum potassium (mmol/L)							-6.11 ± 2.35	-0.104	0.010

Table 4. Linear regression modelling of the QTc interval corrected according to Fridericia's formula and drug serum levels of antipsychotic drugs. A positive β of sex indicates increasing risk in female patients. A p -value < 0.05 was considered statistically significant; aripiprazole, $n = 34$; clozapine, $n = 103$; haloperidol, $n = 26$; olanzapine, $n = 17$; perazine, $n = 24$; quetiapine, $n = 77$; sum of risperidone and its metabolite 9-OH-risperidone/ paliperidone, $n = 72$.

	Model 1			Model 2			Single medication QTcF		
	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p
Genetic QT score (ms)	0.99 ± 0.19	0.179	< 0.001	1.04 ± 0.22	0.186	< 0.001			
Age (years)	0.21 ± 0.06	0.126	< 0.001	0.26 ± 0.07	0.16	< 0.001			
Sex	2.73 ± 1.42	0.067	0.055	3.04 ± 1.73	0.072	0.079			
QT prolonging drugs (n)	1.09 ± 0.58	0.069	0.062	0.66 ± 0.70	0.041	0.348			
Serum potassium (mmol/L)				-6.28 ± 2.35	-0.107	0.008			
Aripiprazole (ng/mL)	-0.02 ± 0.01	-0.052	0.134	-0.02 ± 0.02	-0.045	0.266	-0.02 ± 0.01	-0.038	0.282
Clozapin (ng/mL)	0.00 ± 0.01	0.01	0.773	0.00 ± 0.01	0.003	0.934	0.00 ± 0.01	0.003	0.488
Haloperidol (ng/mL)	0.30 ± 0.17	0.062	0.078	0.33 ± 0.18	0.077	0.061	0.48 ± 0.17	0.101	0.004
Olanzapine (ng/mL)	-0.17 ± 0.08	-0.076	0.027	-0.19 ± 0.08	-0.094	0.019	-0.18 ± 0.08	-0.079	0.025
Perazine (ng/mL)	0.04 ± 0.03	0.052	0.14	0.04 ± 0.03	0.061	0.132	0.04 ± 0.03	0.058	0.101
Quetiapine (ng/mL)	-0.01 ± 0.01	-0.022	0.519	-0.00 ± 0.01	-0.014	0.726	-0.00 ± 0.01	-0.004	0.916
Risperidone + paliperidone (ng/mL)	-0.14 ± 0.06	-0.086	0.014	-0.16 ± 0.06	-0.099	0.014	-0.10 ± 0.06	-0.061	0.083

Table 5. Linear regression modelling of the QTc interval corrected according to Fridericia's formula and number of antipsychotic drugs applied. A positive β of sex indicates increasing risk in female patients. A p -value < 0.05 was considered statistically significant, $n = 804$.

	Model 1			Model 2			Model 3		
	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p	$\beta \pm \text{SEM}$	$\beta(\text{std})$	p
Genetic QT score (ms)	0.99 ± 0.19	0.178	< 0.001	0.99 ± 0.19	0.178	< 0.001	0.97 ± 0.19	0.175	< 0.001
Age (years)	0.25 ± 0.06	0.149	< 0.001	0.25 ± 0.06	0.149	< 0.001	0.26 ± 0.06	0.157	< 0.001
Sex	2.70 ± 1.43	0.066	0.059	2.82 ± 1.42	0.069	0.047	2.51 ± 1.42	0.061	0.078
Antipsychotic drugs (n)	0.94 ± 0.76	0.042	0.220						
1st gen. antipsychotic drugs (n)				2.45 ± 0.92	0.092	0.007			
2nd gen. antipsychotic drugs (n)							-1.73 ± 0.96	-0.062	0.071

small number of patients for which haloperidol serum concentration measurements were available and must be tested for replication in larger samples, yet agree with reports pointing at an increased risk for sudden cardiac death with haloperidol (Beach et al., 2018). No association between individual drug serum concentrations within the therapeutic range and prolongation of the QTc interval could be discerned for the antipsychotic drugs aripiprazole, clozapine, olanzapine, perazine, quetiapine and risperidone after correction for the genetic effect and the number of QT prolonging drugs.

Several limitations apply to the results. The sample represents a naturalistic cohort during inpatient treatment. The individual polygenic QT interval score was based on genome wide significant single nucleotide polymorphisms. Therefore, rare variants or copy number variations were not adequately reflected. No data on the individual QT interval without or prior to initiating drug treatment were available. Due to the naturalistic sample, type and number of comedication were not restricted or limited. Thus, pharmacodynamic drug interactions may have biased the results, for example, by additive effects on the QT interval. We aimed to correct for these effects by accounting for the number of drugs taken and known to induce QT prolongation according to the AZCERT classification (Schwartz and Woosley, 2016), yet no significant effect was observed. Since QT prolongation due to polypharmacy may be modulated by the exact combination of drugs, future studies in larger samples may test to use the AZCERT classification of the combination partners for a better risk stratification (Meid et al., 2017). Moreover, data on cardiac events are unavailable and we used only the QT interval to assess the risk of sudden cardiac death due to widespread clinical adoption. Future studies may therefore consider a detailed cardiac risk estimation by including T-peak to T-end interval and QT dispersion (Acciavatti et al., 2017).

From a clinical point of view, our data suggest that clozapine and quetiapine exhibit the lowest risk for QTc prolongation and hypokalaemia due to the diuretic medication being a strong modifiable factor for QT prolongation due to comedication. Serum concentrations of antipsychotic drugs within the therapeutic range contribute to QTc prolongation rather modestly compared to genetic determinants of the individual patient and age, which possibly also reflects comorbidities. Due to the incomplete correlation between drug dose and drug serum levels, safe daily dose estimates can be hardly given, and we suggest performing therapeutic drug monitoring of antipsychotic drugs on a regular basis (Hiemke et al., 2018). A cardiological assessment might be helpful when repeatedly monitoring an individual QTc prolongation using Fridericia's formula of more than 20ms (one standard deviation of our sample) upon initiating antipsychotic treatment. Taken together, our results underline that careful clinical analysis of all QT prolonging factors is the most important risk-reducing step one can make to minimize the cardiac arrhythmias due to antipsychotic treatment (Beach et al., 2018).

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Role of the sponsors

The supporters had no role in the design, analysis, interpretation, or publication of this study.

Ethical approval

All procedures performed in the analysis involving human participants were in accordance with the ethical standards of the local ethics committee (vote no. 72/99 and 184/11) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patients were recruited and enrolled in the study after written informed consent.

ORCID iDs

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