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Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature

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Abstract

Background: Whether arrhythmia risks will increase if drugs with electrocardiographic (ECG) QT-prolonging properties are combined is generally supposed but not well studied. Based on available evidence, the Arizona Center for Education and Research on Therapeutics (AZCERT) classification defines the risk of QT prolongation for exposure to single drugs. We aimed to investigate how combining AZCERT drug categories impacts QT duration and how relative drug exposure affects the extent of pharmacodynamic drug–drug interactions.

Methods: In a cohort of 2558 psychiatric inpatients and outpatients, we modeled whether AZCERT class and number of coprescribed QT-prolonging drugs correlates with observed rate-corrected QT duration (QTc) while also considering age, sex, inpatient status, and other QTc-prolonging risk factors. We concurrently considered administered drug doses and pharmacokinetic interactions modulating drug clearance to calculate individual weights of relative exposure with AZCERT drugs. Because QTc duration is concentration-dependent, we estimated individual drug exposure with these drugs and included this information as weights in weighted regression analyses.

Results: Drugs attributing a 'known' risk for clinical consequences were associated with the largest QTc prolongations. However, the presence of at least two *versus* one QTc-prolonging drug yielded nonsignificant prolongations [exposure-weighted parameter estimates with 95% confidence intervals for 'known' risk drugs + 0.93 ms (–8.88;10.75)]. Estimates for the 'conditional' risk class increased upon refinement with relative drug exposure and co-administration of a 'known' risk drug as a further risk factor.

Conclusions: These observations indicate that indiscriminate combinations of QTc-prolonging drugs do not necessarily result in additive QTc prolongation and suggest that QT prolongation caused by drug combinations strongly depends on the nature of the combination partners and individual drug exposure. Concurrently, it stresses the value of the AZCERT classification also for the risk prediction of combination therapies with QT-prolonging drugs.

Keywords: cohort study, drug–drug interactions, electrocardiography, psychiatry, QT interval

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Introduction

Whether the prolongation of the electrocardiographic (ECG) rate-corrected QT interval (QTc) is associated with an increased risk for polymorphic ventricular arrhythmia (*torsade de pointes*, TdP)[1,2] and its life-threatening consequences depends on the nature of the compound, its dose, and, thus, the actual exposure of the

patient.[2,3] For an individual risk assessment, it has been suggested to distinguish between three different drug categories of QT-prolonging compounds in the Arizona Center for Education and Research on Therapeutics (AZCERT) classification.[4,5] In the first category, QTc prolongation frequently and dose-dependently causes TdP (class with 'known' risk). Drugs of the second class frequently prolong QTc but TdP rarely ensues ('possible' risk). The third class, finally, compiles compounds whose risk of causing QTc prolongation and TdP depends on the presence of essential cofactors such as hypokalemia, promoting the adverse reaction ('conditional' risk).

While these differences between drugs are well established and likely caused by variable interference of the compounds with cardiac ion currents,[6,7] little is known about the risk of combinations of such drugs and their interactions. There is good evidence for potentially dangerous interactions if a QT-prolonging perpetrator drug decreases the clearance of another QT-prolonging (victim) drug (pharmacokinetic drug–drug interaction, pkDDI), which generally leads to more pronounced QT prolongation because any interference with ion channels is concentration dependent. Such pkDDIs are well documented for drug combinations such as clarithromycin and pimozide,[8] so that the resulting QT prolongation can be caused by only one drug and thus be neither synergistic nor additive. This stresses the need for considering individual exposure to QT-prolonging drugs in any risk assessment strategy.

In contrast to statistical tests for interaction as departure from additive effects,[9] the additive nature of two drugs in a biological sense is thus defined differently: if effects are larger than those observed with the single drugs, the interaction is considered supra-additive or synergistic when the effect of a combination exceeds the sum of effects of the individual compounds.[10] In contrast, if the effect of the combination treatment is in between the sum of the single treatments and the highest single treatment effect, it is considered to be sub-additive. Therefore, a pharmacodynamic drug–drug interaction (pdDDI) in its strict biological sense is only present if synergism or antagonism is observed.

If two compounds do not interact at a pharmacokinetic level, their combination can result in additive effects on one or more ion channels until a maximum (plateau) effect is reached and all available channels are affected (pdDDI).[11] It could also happen that maximum interference is already caused by the first compound, leaving little room for additional modulation of the target ion channel.[12] Finally, in the complexity of cardiac repolarization processes, synergistic or even antagonistic effects could occur if each interaction partner interferes with distinct and synergistic or opposing ion channels.[13] For instance, predictions become challenging due to altered calcium currents or concurrent sodium-channel-blocking activity.[14] In this respect, it is not surprising that both additive and also antagonistic effects on ion channels upon co-administration of QTc-prolonging drugs have been documented[15,16] and that this may translate to null effects on QTc durations.[12] It is therefore questionable whether extrapolation from useful single-drug classification systems to multidrug administration is generally valid and what factors modulate its arrhythmogenic risk.

Considering the multitude of possible drug combinations, the ideal way of answering this question by randomized controlled trials appears hardly feasible. We therefore chose a pharmacoepidemiological approach starting with the AZCERT risk classification to estimate the influence of drug combinations on QT duration and to assess the impact of dose and exposure in a large cohort of unselected psychiatric inpatients and outpatients. In particular, we quantified changes in QT durations depending on the total numbers of QT-prolonging drugs in the patients' medication and compared QT values in patients receiving zero, one, or at least two such drugs. All analyses were further weighted for relative exposure considering dose and comedication.

Methods

Data and study sample

The data of this report originate from a multicenter cross-sectional survey that has recently been described in detail.[17–19] In brief, the study recruited 2558 patients with psychiatric illnesses in Italy from 35 psychiatric services participating in the STAR (Servizi Territoriali Associati per la Ricerca) Network. During a three-month recruitment period, all adult inpatients and outpatients were included if they had full mental capacity, gave written informed consent, and if an ECG was recorded during the hospital stay (inpatients)

or during the recruitment period (outpatients). If more than one ECG was available, only the earliest was considered. No further inclusion criteria were applied, that is, neither specific psychiatric diagnoses nor drug treatment with specific drugs were required. The study was approved by the Ethics Committee of the Azienda Ospedaliera Universitaria Integrata, Verona (Approval Number 2409), and by the Ethics Committee of each participating site.

Socio-demographic and clinical characteristics were extracted from medical records providing covariate information on age, sex, recruitment setting, various risk factors associated with QTc prolongation (electrolyte imbalances of potassium and calcium, current and prior abuse of illicit drugs), ECG recordings, and drug utilization considering relevant modulators of exposure such as dose, pkDDI and their extent. Data are available upon request.

Outcome assessment

In each participating site, standard 12-lead ECGs were recorded and the QT interval was determined by examining lead II with automatic data acquisition; a cardiologist who was blind to the patient's clinical condition confirmed the accuracy of all measurements. Measured QT intervals were corrected for the heart rate using Fridericia's formula[20] to avoid QTc overestimation in patients with heart rates greater than 80 beats per minute (bpm).[21] Qualitative attributes regarding ECG abnormalities were extracted from the ECG report (Table 1) and the analysis data set was accordingly restricted by excluding ECGs with atrial fibrillation, pacemakers, repolarization abnormalities, bundle-branch block, and necrosis or ischemia signs.

Drug exposure

Based on the Anatomical Therapeutic Chemical (ATC) classification system, an ATC code was unequivocally assigned to all drugs (Supplementary Table S1) and using the AZCERT classification, all drugs were further classified according to their risk for actual clinical events (TdP) into categories of high evidence ('known' risk), of evidence of risk only in certain situations ('conditional' risk), and of unclear relevance regarding clinical consequences (i.e. TdP risk) of QTc prolongation ('possible' risk)[5] (Table 2).

Drug dosage. For a very large part of administered drugs, the prescribed daily dose (PDD) could be extracted from medical records (75.3% of all records, 93.6% of included AZCERT drugs). This allowed us to convert drug doses into multiples of the defined daily dose (DDD[22]) by calculating the PDD/DDD ratio as a simple, pragmatic, but reliable way of standardizing drug doses in pharmacoepidemiological research[23,24] (see Supplementary Table S2). This ratio was calculated for all AZCERT drugs. Accordingly, a PDD/DDD ratio of 1.0 indicates that the prescribed dose equals the DDD of that drug, while a ratio higher or lower than 1.0 indicates a relatively higher or lower drug dose than the DDD average.[24] For the remaining small part of drug records without PDD information, a ratio of 1.0 was assumed. The ratio is further used on a multiplicative scale, that is, ratios of AZCERT categories were combined by multiplication.

Approximated drug exposure based on dosage and pharmacokinetic drug–drug interaction. We checked the whole medication of each patient for pkDDIs that influence the clearance of administered QTc-prolonging drugs. Therefore, the AiD-*Klinik*® drug information system (www.aidklinik.de, last accessed on 23 November 2016) was used to determine percentage changes in drug exposure associated with particular combinations. The database contains more than 20,000 DDI entries and is built strictly upon published clinical evidence (i.e. human DDI studies) from which we extracted geometric mean ratios of the areas under the concentration-time curve as a measure for drug exposure changes induced by a combination. The previously calculated PDD/DDD ratio was thus further adjusted with (mean) bioavailability changes induced by the perpetrator drug. As an example, a 50% relative increase in the bioavailability of an AZCERT drug implies that the PDD/DDD ratio was multiplied by 1.5. Finally, each patient was assigned an individually calculated, multiplicative exposure weight of all AZCERT drug categories he or she was exposed to; that weight is composed of PDD/DDD ratios and possibly modulating factors of drug exposure by pharmacokinetically interacting drugs.

Statistical analysis

General framework. Patient characteristics were displayed as frequencies, proportions, or means with standard deviations. The influence of the number of drugs from specific AZCERT

Table 1. Patient characteristics.

Variable		All patients ($n = 2258$)	Patients exposed to AZCERT drug category*		
			'Known' ($n = 793$)	'Conditional' ($n = 941$)	'Possible' ($n = 1216$)
Age at enrolment					
Years	Mean ± SD	48.8 ± 15.2	47.7 ± 15.0	52.3 ± 14.9	48.2 ± 15.0
Sex					
Female	%	53.5	47.9	57.2	51.1
Recruitment setting					
Inpatients	%	77.1	81.3	78.6	73.0
Psychiatric diagnosis according to World Health Organization[27]					
Organic (including symptomatic) mental disorders	%	1.50	1.14	1.50	1.25
Mental and behavioural disorders due to psychoactive substance use	%	3.03	3.04	2.99	1.50
Schizophrenia, schizotypal and delusional disorders	%	35.8	39.2	28.7	41.6
Mood (affective) disorders	%	39.4	37.6	45.6	39.0
Neurotic, stress-related and somatoform disorders	%	7.04	7.86	7.16	4.49
Behavioural syndromes associated with physiological and physical factors	%	0.83	0.51	1.07	0.66
Disorders of adult personality and behaviour	%	10.7	9.25	11.3	10.2
Mental retardation	%	1.34	1.27	1.18	1.25
Disorders of psychological development	%	0.08	0.00	0.11	0.08
Behavioural and emotional disorders (usual onset in childhood and adolescence)	%	0.24	0.13	0.32	0.00
Heart rate					
(bpm)	Mean ± SD	79.1 ± 15.3	79.1 ± 15.8	77.9 ± 15.1	80.0 ± 15.5
QTc (Fridericia corrected)					
(ms)	Mean ± SD	400.3 ± 32.0	401.8 ± 32.2	403.6 ± 34.5	396.9 ± 32.5
Prolonged QTc§	%	2.70	1.77	3.93	2.38
Abnormal laboratory values‡					
Potassium	%	5.35	4.29	4.10	4.18
Calcium	%	4.57	2.30	3.66	2.95

Table 1. (Continued)

Variable		All patients ($n = 2258$)	Patients exposed to AZCERT drug category*		
			'Known' ($n = 793$)	'Conditional' ($n = 941$)	'Possible' ($n = 1216$)
Alcohol or substance abuse (illicit drugs)‡					
Prior	%	18.5	20.1	18.4	15.4
Recent	%	10.6	7.73	9.19	3.54
Drug exposure					
Total drug number per patient	Mean ± SD	3.51 ± 2.11	3.95 ± 2.18	4.50 ± 2.18	3.88 ± 1.98
AZCERT 'known' risk drug number per patient	Mean ± SD	0.34 ± 0.54	1.10 ± 0.32	0.23 ± 0.47	0.23 ± 0.45
AZCERT 'conditional' risk drug number per patient	Mean ± SD	0.44 ± 0.64	0.31 ± 0.59	1.20 ± 0.45	0.35 ± 0.58
AZCERT 'possible' risk drug number per patient	Mean ± SD	0.57 ± 0.68	0.37 ± 0.57	0.45 ± 0.63	1.20 ± 0.46
Multiplicative weight of relative exposure with drugs of respective categories	Mean ± SD		0.87 ± 0.96	0.99 ± 0.90	1.07 ± 1.60
ECG characteristics§					
Normal ECG	%	70.1	68.7	65.7	69.0
Mild abnormalities in repolarization‖	%	10.0	10.3	10.9	10.7
Bundle-branch block or abnormality‖	%	9.12	8.85	10.12	8.44
Atrial fibrillation‖	%	0.25	0.33	0.29	0.10
(Supra)ventricular extrasystoles	%	1.19	0.98	1.03	1.54
Atrial enlargement	%	0.59	0.66	0.59	0.62
Axial deviation	%	4.07	5.41	5.87	4.94
QTc interval > 500 ms	%	0.81	0.82	0.88	0.62
Necrosis or ischemia signs‖	%	1.48	1.15	1.91	1.65
Ventricular hypertrophy	%	1.53	2.30	2.05	1.44
Pacemaker	%	0.38	0.49	0.44	0.51

*Due to exposure with several AZCERT classes, subgroup numbers may total >2258.
§According to the European regulatory guidelines.[31]
‡Summarized as a composite binary variable in statistical models.
§Percentages may not total 100, due to rounding.
‖Corresponding cases were excluded from the analysis set for statistical models (in addition to an implausible measurement of QT measurement of 165.9 ms).
AZCERT, Arizona Center for Education and Research on Therapeutics; SD, standard deviation; ECG, electrocardiogram; QTc, corrected QT interval time; bpm, beats per minute; ms, milliseconds.

Table 2. Patient exposure to QTc-prolonging drugs according to the AZCERT classification.

AZCERT risk category	Drug name	Patients in total (*n*)	Patients with coexposure to further AZCERT drugs of the categories		
			'Known' (*n*)	'Conditional' (*n*)	'Possible' (*n*)
'Known'	Amiodarone	4	1	2	0
	Azithromycin	2	1	1	0
	Chlorpromazine	114	26	32	37
	Ciprofloxacin	8	3	3	3
	Citalopram	109	16	31	39
	Domperidone	8	2	5	4
	Donepezil	2	0	2	0
	Escitalopram	102	10	28	41
	Fluconazole	2	1	1	0
	Haloperidol	414	41	79	111
	Levofloxacin	3	0	1	1
	Levomepromazine	61	19	18	35
	Methadone	25	7	14	6
	Ondansetron	1	0	0	0
	Sulpiride	3	0	3	0
'Conditional'	Amantadine	1	1	1	0
	Amisulpride	35	5	16	20
	Amitriptyline	33	4	9	5
	Fluoxetine	47	7	9	17
	Furosemide	67	26	25	29
	Hydrochlorothiazide	52	15	20	28
	Hydroxychloroquine	1	1	1	1
	Indapamide	1	0	1	0
	Ivabradine	1	0	0	1
	Metoclopramide	5	1	4	0
	Pantoprazole	55	25	30	29
	Paroxetine	122	13	41	38
	Quetiapine	388	92	113	126
	Ritonavir	9	3	4	2
	Sertraline	220	34	59	83
	Trazodone	82	18	25	38
	Ziprasidone	12	2	5	7
'Possible'	Alfuzosin	7	2	5	2
	Aripiprazole	195	51	60	65
	Asenapine	38	6	12	15
	Atazanavir	2	0	1	1
	Clomipramine	62	9	30	31

Table 2. (Continued)

AZCERT risk category	Drug name	Patients in total (*n*)	Patients with coexposure to further AZCERT drugs of the categories		
			'Known' (*n*)	'Conditional' (*n*)	'Possible' (*n*)
	Clozapine	162	34	44	43
	Imipramine	2	0	1	0
	Lithium	140	22	54	76
	Mirtazapine	101	29	41	43
	Nortriptyline	2	0	2	1
	Olanzapine	329	86	64	75
	Paliperidone	62	8	12	11
	Rilpivirine	1	0	1	1
	Risperidone	215	32	43	41
	Saquinavir	1	0	1	1
	Tamoxifen	5	2	1	3
	Tetrabenazine	1	0	0	1
	Trimipramine	2	0	2	1
	Venlafaxine	131	15	52	50

AZCERT, Arizona Center for Education and Research on Therapeutics; QTc, corrected QT interval time.

categories was determined by a linear model that further adjusted for sex, age, recruitment site (inpatient or outpatient), and a binary variable indicating known risk factors for QTc prolongation (potassium or calcium imbalances, or current or prior abuse of illicit drugs). To account for relative exposure beyond the drug counts, calculated multiplicative weights for AZCERT categories of individual patients were applied in corresponding weighted regression analyses. We compared weighted and standard linear models of equal model equations with the Davidson–MacKinnon $\mathcal{J}$-test.[25] All tests were two tailed, 95% confidence intervals (CI) were calculated, and p values < 0.05 were considered statistically significant. Statistical analyses were performed using the R software/environment version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria, 2015).

The study's primary objectives comprised two parts, that is, to determine risks associated with the drug number of QT-prolonging drugs and to determine associated risks for distinct pair-wise group comparisons (e.g. one *versus* at least two drugs). The main analyses focused on the AZCERT categories of 'known' and 'conditional' risk, for which actual evidence of relevant clinical outcomes (TdP) exists.[5]

Continuous predictors. To address the study objectives' first part, drug numbers of respective AZCERT categories were included as continuous variables into linear models, from which QTc duration was predicted in dependence of the drug number. Because the main effects in underlying models with interaction terms between the three AZCERT categories cannot be interpreted in isolation, we also provided results from main effects regression models to facilitate direct interpretation (Supplementary Table S3). As a further step beyond combinations within a particular risk category, we aimed to investigate the role of 'conditional' risk drugs in the presence of a 'known' risk drug, and vice versa. We therefore extended model predictions to a situation when one drug from the other category is already present.

Categorical predictors. To further investigate the difference between zero, one, or more drugs of a given category, the drug numbers were accordingly categorized and analyzed in otherwise equally parameterized models by means of

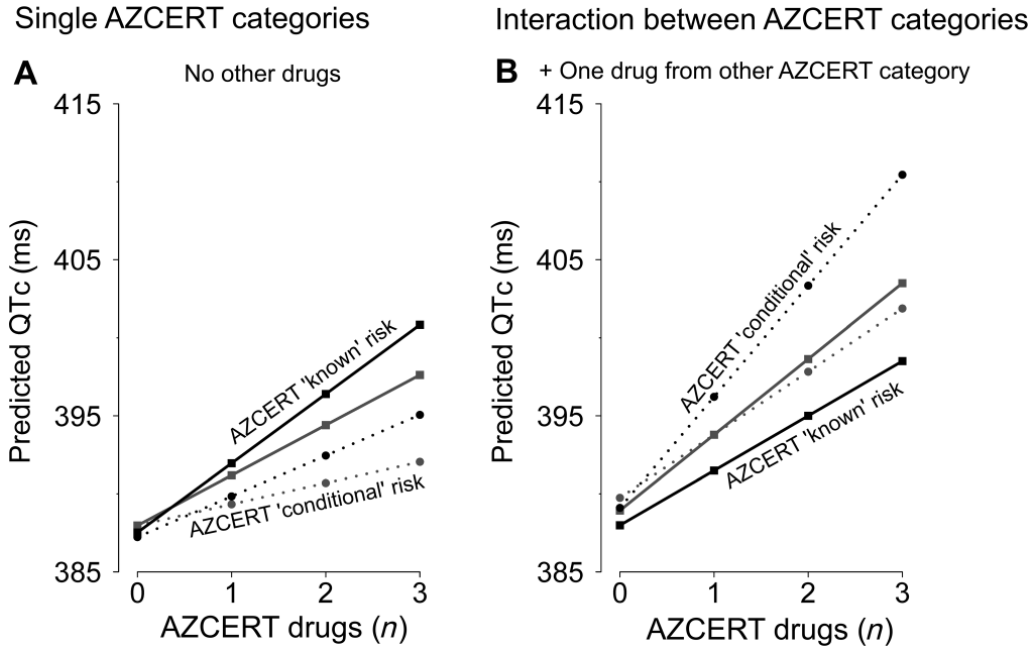

Figure 1. Predicted change in corrected QT (QTc) interval duration for different AZCERT drug categories. To predict QTc values, the AZCERT drug counts of 'known' (▪, solid line) and 'conditional' risk (•, dotted line) were varied, while other covariates were fixed. Predictions were based on weighted regression models (black), which accounted for individual drug doses and pharmacokinetic drug–drug interaction modulating drug exposure, and on unweighted regression models (gray). The left plot (A) predicts QTc duration in the presence of the number of drugs from the respective AZCERT category only, while the right plot (B) depicts the predicted QTc intervals in the presence of one drug from the other category.
AZCERT, Arizona Center for Education and Research on Therapeutics; ms, milliseconds.

multiple comparison procedures. Therefore, we conducted multiple pair-wise comparisons and trend tests using corresponding vectors of contrast coefficients: Tukey contrasts were used to provide many-to-many comparisons and with Marcus contrasts, we tested ordered risk trends between the distinct groups of zero, one, and two or more drugs. Appropriate adjustment for multiple testing is guaranteed with these sets of orthogonal contrasts.[26]

Results

About one in three of the 2558 eligible psychiatric patients (Table 1) was exposed to drugs with 'known' risk for TdP according to the AZCERT classification, and 44% of the patients used drugs of the category with a 'conditional' risk for TdP. Coprescription of more than one drug of the same or another AZCERT risk category was present in about one in five patients. The mean QTc values in the analysis set were 395 ± 29.6 ms (range: 232–474) in male patients and 401 ± 29.5 ms (range: 262–493) in female patients. Table 2 shows the most frequently used drugs for each AZCERT category and the number of exposed patients that concomitantly administered further drugs of the respective categories. Excessive doses above a PDD/DDD ratio of 3.0 were present in approximately 2.4% of antipsychotic drugs.

The additive nature was studied in continuous predictor models with actual drug numbers and in categorical predictor models with categories of zero, one, or more drugs. Continuous QTc predictions considered the number of co-administered QTc-prolonging drugs of 'known' and 'conditional' AZCERTs risks in linear models. Predicting the QTc interval in situations with only drugs of one AZCERT category yielded significant increases with the number of drugs attributed a 'known' risk (Supplementary Table S2), which translated into an increasing slope only after we accounted for relative exposure by weighting regressions (Figure 1A). Of note, a significant negative slope was obtained for the 'possible' risk category (Supplementary Figure S1, Supplementary Table S3). Thereafter, we considered a situation with one drug of the other category already present (i.e. one drug of 'known' or

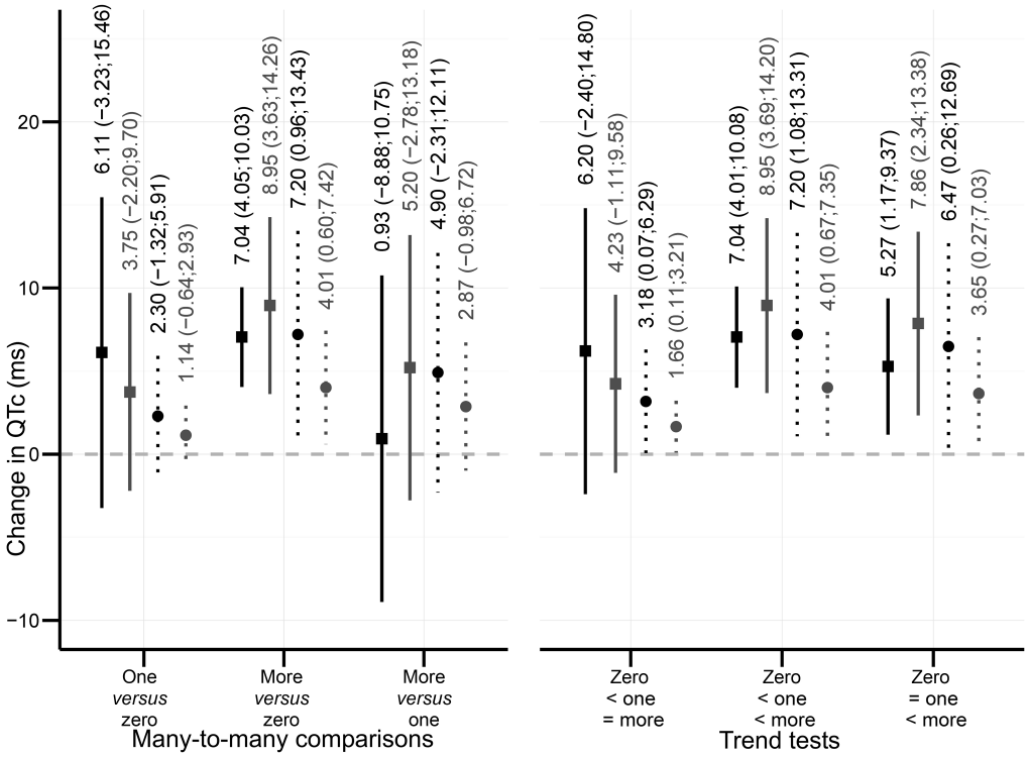

Figure 2. Relative change in corrected QT (QTc) interval duration upon presence of drugs from different AZCERT categories (▪ solid line: 'known' risk; • dotted line: 'conditional' risk). The frequencies of AZCERT drugs were categorized into groups of 'zero', 'one', and 'more' (at least two) drugs. Pair-wise many-to-many comparisons (Tukey contrasts) and trend tests (Marcus contrasts)[26] were applied in corresponding linear models with these categorical predictors (gray: standard linear model; black: weighted linear model with relative drug exposure weights).

'conditional' risk, respectively). Here, the slopes for both AZCERT categories increased while the most pronounced increase comparing raw and exposure-weighted regression curves was manifest for drugs of the 'conditional' risk category (Figure 1B). Also in this situation, weighting refined effects in an exposure-dependent fashion and the difference to unweighted estimates demonstrated the impact of relative drug exposure (model comparison $p = 0.002$).

To evaluate whether QTc duration increases with exposure to more than one QTc-prolonging drug, categories based on AZCERT drug numbers were tested in pair-wise group comparisons and trend tests (Figure 2).[26] Strong effects were obtained for comparisons between two or more drugs and no AZCERT drugs for categories of 'known' and 'conditional' risk. While a trend towards increasing QTc duration was apparent for both categories, the dedicated pair-wise comparisons between two or more and one drug of the respective category were not significant, as were comparisons between one and zero drugs. Upon considering weights of relative exposure, effect estimates of drugs with an attributed 'conditional' risk generally rose.

Discussion

The results of this exploratory investigation assessing the potential contribution of pkDDI and pdDDI to drug-induced QTc prolongation are in line with existing risk classifications for single-drug administration such as AZCERT; when only a single AZCERT class is considered, drugs attributed a 'known' risk for TdP also accounted for the largest changes in QTc duration (Figure 1A), whereas such an association was less pronounced for drugs with 'conditional' risk and absent for those with 'possible' risk (Supplementary Table S2, Supplementary Figure S1). These findings therefore support the concept of distinguishing different categories of QTc-prolonging drugs as propagated by AZCERT, regardless of co-administered additional AZCERT drugs.

Moreover, it endorses the denotation of 'conditional' risk which apparently depends on additional risk factors (Figure 1B), indeed.

Our analysis revealed that the nature of the combination partners substantially influenced the combinations' QTc-prolonging potential; in a biological sense, combinations of AZCERT drugs with 'possible' risk had no additional risk of QTc prolongation and appeared to be even antagonistic. In contrast, with increasing number of members of the 'conditional' and 'known' risk classes, the risk of QTc prolongation appeared additive, and its magnitude was dependent on the presence of further risk factors, such as further drugs in situations when categories were mixed.

While our analysis did not reveal synergistic phenomena, any prolongation can be relevant in the individual case (see Supplementary Figure S3). It is therefore noteworthy that clinical monitoring should be based on individual risk thresholds (affected by further risk factors such as genetic predisposition, sex, age and bradycardia, among others) and thereafter consider net drug-induced contributions rather than mere drug numbers. As a consequence of QTc prolongation being concentration dependent, prescription warnings should be issued cautiously, because additive effects may be clinically negligible if drug doses are appropriately chosen. This generally holds for concentration-dependent effects, for which many examples from other drug classes also exist.[28] Thus, patients on high-risk drugs can have a normal ECG and stay perfectly well.[29]

Our findings confirm the expectation that extrapolation of any single-drug risk to multidrug administration is not generally valid for all combinations.[30] The present analysis supports this notion by analyses of QTc durations and also underlines the importance of quantitative drug exposure for risk estimation. These findings are consistent with the results from the Rotterdam study that equally found no systematically increased QTc duration when two or more such drugs were administered.[31] Compared with our cohort of psychiatric patients, we observed somewhat lower frequencies of prolonged QTc duration according to the European regulatory guidelines.[32] Inpatient status was strongly associated with QTc duration (Supplementary Table S3), which certainly reflects a different comorbidity level, but may also imply more frequent parenteral routes of administration with a higher risk for prolonged QTc durations.[2,33] Besides, ECG abnormalities were relatively frequent (Table 1), but effect estimates remained robust upon their inclusion or removal in sensitivity analyses (data not shown). Similar to the Rotterdam study, our comparison of two or more *versus* one risk drug did not yield significant prolongations with point estimates similar to the comparison between one and zero drugs. While this as a population mean cannot exclude synergistic interactions between distinct individual pairs or combinations, it provides considerable evidence that synergism is not the standard mode of pdDDI for QTc-prolonging drugs. As shown by the steep rise in the risk of additional drugs upon assigning more weight to high drug exposure, drug exposure appears to be a decisive element for specific warnings and that dose adaptation can be useful to manage individual risks.

Individual risks are modulated by several cofactors, such as advanced age, female sex, electrolyte disturbances, genetic predisposition for long-QT syndrome, structural heart disease, bradycardia, drugs interfering with cardiac ion channels and electrolyte balance, and combinations of these factors.[7] Experimental evidence of the risks of combining several QTc-prolonging drugs is limited; the best evidence is currently available for pkDDI, which increases both the exposure of a QTc-prolonging drug and its QTc-prolonging effect (for a comprehensive literature review of controlled trials, see Wisniowska *et al.*[34]). Nevertheless, infinite prolongation of the QT interval is not possible because every exposure–response relationship involving countable targets is saturable.[11] Once maximum QTc prolongation is reached, adding a further drug acting *via* the same QTc-prolonging mechanism might not further increase the QTc-attributed arrhythmia risk. In line with the concept of plateau effects is a validated prediction model yielding similar odds of QTc prolongation for patients receiving one *versus* two or more QTc-prolonging drugs.[35] Taken together, the nature and concentration of the administered QTc-prolonging drug and the comedication affecting its clearance appear more important than the net number of such drugs.

In fact, our findings (Figure 1) suggest that not all combinations of QTc-prolonging drugs have the same propensity to prolong the QTc duration. This also applies to 'possible' QTc-prolonging drugs that were even associated with shorter QTc values, which may appear paradox (Supplementary Figures S1 and S2). However, Silvestre and

coworkers also reported QTc interval shortening for some of the 'possible risk' drugs.[36] This finding is supported by examples where effects on delayed rectifier potassium channel are obviously compensated by modulations of late sodium currents,[37] resulting in increased risk upon relief of the channel block and thus potentially reduced risk during the compensating channel block. The notion that mechanistic considerations are predictive for QTc prolongation of drug combinations should be further scrutinized because it could well explain differences between different drug combinations.

Beyond statistical significance, results have to be put into a clinical perspective. Available benchmarks include a mean QTc change above 5 ms to identify drugs as being pro-arrhythmic[38] and each 10 ms increase in Bazett-corrected QTc intervals is expected to elevate the risk for cardiac events by 6%.[39] However, both assumptions do not consider established differences in the risks of different drugs as, for example, defined in the AZCERT risk classification and may thus be too broad and general at the expense of specificity. Moreover, the value of these indicators in the risk assessment of QTc-prolonging drugs could be only relevant for (i) dedicated combinations of AZCERT 'known' risk drugs and for (ii) 'conditional' risk drugs only in the presence of further risk factors (Figures 1 and 2). Concerning the risk of drug-induced TdP, QTc prolongations $>$ 500 ms[4] (deduced from studies with congenital long-QT syndromes[40,41]) or net individual increases of $>$60 ms[2,42] can be observed when additional risk factors, such as advanced age, bradycardia or electrolyte disturbances coincide or accumulate.[43–45]

Additive or even synergistic risks of underlying pdDDI should not be generally postulated unless evidence for a specific drug combination actually exists. To avoid poor alert specificity, over-alerting, and thus poor alert acceptance,[46] warnings should be specific, tailored, and restricted to thoroughly investigated combinations or at most to multidrug combinations involving drugs with a 'known' risk. Otherwise, indiscriminate warnings in guidelines, product labels, or electronic prescribing systems will produce alert frequencies in the percent range.[47,48] Overestimated risks may prompt physicians to unjustifiably withhold potentially effective therapies.

We would like to stress a number of relevant limitations. Conceptually, our data originate from a cross-sectional design with no relevant clinical endpoints available beyond a single QTc measurement as an imperfect surrogate for assessing the risk for TdP; nevertheless, it is a currently accepted marker for possible TdP arrhythmia and its monitoring is generally used to identify risk and modify therapies.[2,7,49] To avoid bias, we always used the first recorded ECG, which was closest to the list of drugs considered in our analyses, even though for some patients, more than one ECG was available. Concerning independent (predictor) variables, it would have been desirable to have more details at hand. For example, only the dichotomous variable describing abnormal electrolyte status was available without specific information on the exact value or at least the direction of the deviation from the normal range. In addition, a precise value for exposure was neither available; therefore, exposure and exposure modulation had to be approximated from population means and mean changes. As basically true for all pharmacoepidemiological analyses, the reason for being exposed to a specific drug or not (i.e. indication, contraindication, disease severity and adherence) can be of importance for the association with the outcome of interest. In particular, high-risk coprescriptions could have been avoided by skilful prescribing. However, because QTc duration as a surrogate for TdP risk assessment is only seldom considered in routine care,[50,51] this aspect is unlikely to affect prescription in otherwise low-risk populations. Moreover, also due to the observational study design, we could not adjust our sample size to provide sufficient power for certain comparisons, such as pair-wise group comparisons between one and two or more drugs of an AZCERT class. Finally, because the timing of QTc measurements relative to the timing of drug administration is not known, inconsistent time points of QTc measurements might have influenced the results.

Conclusion

Accounting for relative exposure differences with QTc-prolonging drugs significantly improved QTc interval predictions when single or multiple drugs with QTc-prolonging potential were administered. In contrast, the pharmacodynamic contribution of multiple QTc-prolonging drugs was less pronounced and appeared to depend on the AZCERT risk classification. Clearly, additive risks were only observed when drugs with an attributed 'known' risk for TdP were involved. In these cases, and also drugs associated with a

'conditional' risk, excessive drug exposures (e.g. high doses or pkDDI) should be avoided and, if not avoidable, a close ECG monitoring is advisable. This may be a first step to more specific warnings by avoiding false alerts in computerized alert systems and to identify patients who really require close ECG monitoring.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Supplementary Material

Supplementary material is available for this article online.

References

1. Haddad PM and Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; 62: 1649–1671.
2. Drew BJ, Ackerman MJ, Funk M, *et al.* Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2010; 55: 934–947.
3. De Bruin ML, Langendijk PN, Koopmans RP, *et al.* In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs. *Br J Clin Pharmacol* 2007; 63: 216–223.
4. Arizona Science Foundation. CredibleMeds®, https://crediblemeds.org/index.php?rf=US (accessed 23 November 2016).
5. Schwartz PJ and Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. *J Am Coll Cardiol* 2016; 67: 1639–1650.
6. Vlachos K, Georgopoulos S, Efremidis M, *et al.* An update on risk factors for drug-induced arrhythmias. *Expert Rev Clin Pharmacol* 2016; 9: 117–127.
7. Frommeyer G and Eckardt L. Drug-induced proarrhythmia: risk factors and electrophysiological mechanisms. *Nat Rev Cardiol* 2016; 13: 36–47.
8. Desta Z, Kerbusch T and Flockhart DA. Effect of clarithromycin on the pharmacokinetics and

pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; 65: 10–20.

9. Ahlbom A and Alfredsson L. Interaction: a word with two meanings creates confusion. *Eur J Epidemiol* 2005; 20: 563–564.
10. Chou TC. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. *Pharmacol Rev* 2006; 58: 621–681.
11. Mehta R, Green M, Patel B, *et al.* Concentration-QT analysis of the randomized, placebo- and moxifloxacin-controlled thorough QT study of umeclidinium monotherapy and umeclidinium/vilanterol combination in healthy subjects. *J Pharmacokinet Pharmacodyn* 2016; 43: 153–164.
12. Charbit B, Alvarez JC, Dasque E, *et al.* Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study. *Anesthesiology* 2008;109: 206–212.
13. Titier K, Girodet PO, Verdoux H, *et al.* Atypical antipsychotics: from potassium channels to torsade de pointes and sudden death. *Drug Saf* 2005; 28: 35–51.
14. Gintant GA, Gallacher DJ and Pugsley MK. The 'overly-sensitive' heart: sodium channel block and QRS interval prolongation. *Br J Pharmacol* 2011; 164: 254–259.
15. Margulis M and Sorota S. Additive effects of combined application of multiple hERG blockers. *J Cardiovasc Pharmacol* 2008; 51: 549–552.
16. Friemel A and Zunkler BJ. Interactions at human ether-a-go-go-related gene channels. *Toxicol Sci* 2010; 114: 346–355.
17. Nose M, Bighelli I, Castellazzi M, *et al.* Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study. *Epidemiol Psychiatr Sci*. Epub ahead of print 15 October 2015.
18. Barbui C, Bighelli I, Carra G, *et al.* Antipsychotic dose mediates the association between polypharmacy and corrected QT interval. *PLoS One* 2016; 11: e0148212.
19. Carra G, Crocamo C, Bartoli F, *et al.* First-generation antipsychotics and QTc: any role for mediating variables? *Hum Psychopharmacol* 2016; 31: 313–318.
20. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. *Ann Noninvasive Electrocardiol* 2003; 8: 343–351.
21. Vandenberk B, Vandael E, Robyns T, *et al.* Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc* 2016; pii: e003264.
22. World Health Organisation. ATC classification index with DDDs 2014. World Health Organisation Collaborating Centre for Drug Statistics Methodology, http://www.whocc.no/ddd/definition_and_general_considera/ (accessed 23 November 2016).
23. Nose M and Barbui C. A simple approach to manage dosages in drug-epidemiology research. *Epidemiol Psichiatr Soc* 2008; 17: 186–187.
24. Nose M, Tansella M, Thornicroft G, *et al.* Is the defined daily dose system a reliable tool for standardizing antipsychotic dosages? *Int Clin Psychopharmacol* 2008; 23: 287–290.
25. Davidson R and MacKinnon JG. Several tests for model specification in the presence of alternative hypotheses. *Econometrica* 1981; 49: 781–793.
26. Hothorn T, Bretz F and Westfall P. Simultaneous inference in general parametric models. *Biom J* 2008; 50: 346–363.
27. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines, http://apps.who.int/classifications/icd10/browse/2016/en#/V (accessed 23 November 2016).
28. Mayer T, Kopitz J, Plaschke K, *et al.* Limitations of the anticholinergic activity assay and assay-based anticholinergic drug scales. *Am J Geriatr Psychiatry* 2016; 24: 1182–1188.
29. Thomas SH and Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. *Br J Clin Pharmacol* 2016; 81: 420–427.
30. Meid AD, von Medem A, Heider D, *et al.* Investigating the additive interaction of QT-prolonging drugs in older people using claims data. *Drug Saf* 2017; 40: 133–144.
31. Niemeijer MN, van den Berg ME, Franco OH, *et al.* Drugs and ventricular repolarization in a general population: the Rotterdam Study. *Pharmacoepidemiol Drug Saf* 2015; 24: 1036–1041.
32. Van Noord C, Straus SM, Sturkenboom MC, *et al.* Psychotropic drugs associated with corrected QT interval prolongation. *J Clin Psychopharmacol* 2009; 29: 9–15.
33. Somberg JC, Preston RA, Ranade V, *et al.* QT prolongation and serum sotalol concentration are highly correlated following intravenous and oral sotalol. *Cardiology* 2010; 116: 219–225.
34. Wisniowska B, Tylutki Z, Wyszogrodzka G, *et al.* Drug-drug interactions and QT prolongation

as a commonly assessed cardiac effect – comprehensive overview of clinical trials. *BMC Pharmacol Toxicol* 2016; 17: 12.

35. Tisdale JE, Jaynes HA, Kingery JR, *et al.* Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes* 2013; 6: 479–487.

36. Silvestre JS, O'Neill MF and Prous JR. Evidence for a crucial modulating role of the sodium channel in the QTc prolongation related to antipsychotics. *J Psychopharmacol* 2014; 28: 329–340.

37. Kuryshev YA, Bruening-Wright A, Brown AM, *et al*. Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. *J Cardiovasc Pharmacol* 2010; 56: 420–430.

38. International Conference on Harmonisation (ICH). E14 Guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (2005), https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf (accessed 23 November 2016).

39. Zareba W, Moss AJ, Schwartz PJ, *et al.* Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. *N Engl J Med* 1998; 339: 960–965.

40. Priori SG, Schwartz PJ, Napolitano C, *et al.* Risk stratification in the long-QT syndrome. *N Engl J Med* 2003; 348: 1866–1874.

41. Sauer AJ, Moss AJ, McNitt S, *et al.* Long QT syndrome in adults. *J Am Coll Cardiol* 2007; 49: 329–337.

42. Trinkley KE, Page RL II, Lien H, *et al.* QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin* 2013; 29: 1719–1726.

43. France NP and Della Pasqua O. The role of concentration-effect relationships in the assessment of QTc interval prolongation. *Br J Clin Pharmacol* 2015; 79: 117–131.

44. Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. *Pacing Clin Electrophysiol* 1998; 21: 1029–1034.

45. Rabkin SW. Impact of age and sex on QT prolongation in patients receiving psychotropics. *Can J Psychiatry* 2015; 60: 206–214.

46. Seidling HM, Klein U, Schaier M, *et al*. What, if all alerts were specific – estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014; 83: 285–291.

47. Curtis LH, Ostbye T, Sendersky V, *et al.* Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med* 2003; 114: 135–141.

48. Schachtele S, Tumena T, Gassmann KG, *et al.* Co-prescription of QT-interval prolonging drugs: an analysis in a large cohort of geriatric patients. *PloS One* 2016; 11: e0155649.

49. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; 350: 1013–1022.

50. Warnier MJ, Rutten FH, Souverein PC, *et al.* Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? The example of haloperidol. *Pharmacoepidemiol Drug Saf* 2015; 24: 701–708.

51. Choo WK, Turpie D, Milne K, *et al.* Prescribers' practice of assessing arrhythmia risk with QT-prolonging medications. *Cardiovasc Ther* 2014; 32: 209–213.