REVIEW ARTICLE

QTc Prolongation by Psychotropic Drugs and the Risk of Torsade de Pointes

Katharina Wenzel-Seifert, Markus Wittmann, and Ekkehard Haen

SUMMARY

Introduction: Many psychotropic drugs can delay cardiac repolarization and thereby prolong the rate-corrected QT interval (QTc). A prolonged QTc often arouses concern in clinical practice, as it can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP).

Method: We searched PubMed for pertinent literature on the risk of QTc prolongation and/or TdP associated with commonly used psychotropic drugs.

Results: Thioridazine and ziprasidone confer the highest risk of QTc prolongation and/or TdP. There is also a clinically significant risk associated with haloperidol given intravenously in high doses. TdP has been reported in a few cases in association with the use of newer antipsychotic drugs (mainly quetiapine and amisulpride), most of the tri- and tetracyclic antidepressants, and the selective monoamine reuptake inhibitors citalopram, fluoxetine, paroxetine, and venlafaxine. As a rule, however, QTc prolongation and/or TdP occur only in the presence of multiple additional risk factors, such as age over 65 years, pre-existing cardiovascular disease, bradycardia, female sex, hypokalemia, hypomagnesemia, a supratherapeutic or toxic serum concentration, or the simultaneous administration of other drugs that delay repolarization or interfere with drug metabolism.

Conclusion: Before prescribing a psychotropic drug, the physician should carefully assess its risks and benefits to avoid this type of adverse reaction, particularly when additional risk factors are present. The ECG and electrolytes should be regularly monitored in patients taking psychotropic drugs.

► Cite this as:
Wenzel-Seifert K, Wittmann M, Haen E: QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011; 108(41): 687–93.
DOI: 10.3238/arztebl.2011.0687

Zentrum Pharmakologie und Toxikologie, Medizinische Hochschule Hannover: Dr. med. Wenzel-Seifert

Klinische Pharmakologie; Klinik- und Poliklinik für Psychiatrie, Psychosomatik und Psychotherapie der Universität Regensburg: Dr. med. Wittmann, Prof. Dr. med. Dr. med. habil. Dr. rer. nat. Haen

Many drugs prolong ventricular repolarization, potentially giving rise to a prolonged QT interval in the electrocardiogram (ECG) and to the polymorphic ventricular tachyarrhythmia known as torsade de pointes (TdP). TdP is usually self-limited and typically manifests itself in convulsions, dizziness, and syncope. It can, however, lead to ventricular fibrillation and sudden cardiac death.

Drugs that prolong the QT interval bind to cardiac potassium channels (I_{Kr}, also known as HERG channels because of the associated genetic locus, the human ether-a-go-go related gene). The resulting blockade of potassium efflux from cardiomyocytes prolongs the repolarization phase. In the congenital long-QT syndrome (LQTS 2), a mutation of the I_{Kr} gene causes prolongation of the QT interval (1).

When class IC and class III antiarrhythmic drugs (sotalol, flecainide, propafenone) are used, the risk of TdP is correlated with the extent of prolongation of the QT interval. There is no such correlation, however, for other repolarization-prolonging drugs. Dose-dependent QT prolongation has been described, in particular, for classic antipsychotic drugs and tricyclic antidepressants, yet these drugs do not necessarily elevate the risk of TdP: Sertindole is a case in point (1, 2).

Calculation of the QTc

The QT interval is difficult to measure when the T wave is of low amplitude, so that the point at which it ends is hard to define. QT intervals should be measured manually on a 12-lead ECG (usually in limb lead II), and the mean measurement from 3 to 5 heartbeats should be taken as the final value (3). As repolarization is faster when the heart beats more rapidly, the QT interval should also be corrected for the heart rate. The most commonly used correction formula, that of Bazett ($QTc = QT/RR^{0.5}$), should only be used when the heart rate lies in the relatively narrow range of 60 to 80 beats per minute. For higher heart rates, the Fridericia correction formula is suitable ($QTc = QT/RR^{0.33}$). There is considerable intra-individual variability of the QTc: multiple studies have shown that it can vary by anywhere from 76 to 102 ms over the course of 24 hours. In normal persons, the mean QTc length is roughly 400 ms. The upper limit of normal is 460 ms for women, and 450 ms for men. QTc intervals longer than 500 ms are considered to be a major risk factor for the development of TdP (4, 5).

Risk factors

A patient's risk of QTc prolongation or of TdP depends not only on medications taken, but also in large measure on individual factors and other environmental influences (6, 7):

- age over 65 years;
- female sex (longer QTc interval than men and twice the risk of drug-induced TdP);
- myocardial hypertrophy (e.g., in arterial hypertension);
- congenital QT syndrome;
- bradycardia (leads *per se* to QTc prolongation; sinus bradycardia; 2nd- and 3rd-degree atrioventricular block);
- electrolyte disturbances (hypokalemia, hypomagnesemia);
- high plasma concentrations of the offending drug because of overdose, intoxication or inhibition of drug metabolim by concomitantly administered drugs and/or reduced drug clearance due to renal or hepatic insufficiency, or because of rapid infusion of the drug.

In a study of 77 cases of drug-associated TdP, two or more additional risk factors were present in 85%: heart disease (77%), age over 65 (54%), female sex (69%), and hypokalemia (30%) (8).

Methods

There have not been any systematic studies of the effect of classic neuroleptic drugs or older antidepressants on the QTc interval. It was only in connection with the approval of newer drugs that the drug approval agencies began to require that such studies be performed. In this article, we estimate the torsadogenic risk of psychotropic drugs on the basis of published clinical studies, database evaluations, and case reports. We searched PubMed for articles containing the generic names of various drugs and drug classes (e.g., "antipsychotic," "antidepressant") along with the terms "QT," "torsade(s) de pointes," "TdP," "cardiotoxicity," and "sudden death." In the *Table*, drugs are listed in order of decreasing risk of TdP. In constructing the *Table,* we gave the highest priority to the evaluations of the University of Arizona's Center for Education and Research on Therapeutics (Arizona CERT), which regularly publishes updated lists of drugs associated with varying risks of TdP on the website www.torsades.org (9). We gave secondary priority to the presence and number of case reports of TdP for each drug (especially when TdP arose at therapeutic doses), as well as to the extent of QTc prolongation (7, 10).

As TdP is rare, its incidence cannot be accurately estimated on the bases of controlled studies, databases of adverse reaction reporting systems, or assessment of published case reports. QTc prolongation and TdP occurrences have been a focus of attention for no more than 10 to 15 years, and many TdP cases escape clinical detection because no ECG is recorded. Moreover, new types of antipsychotic and antidepressant drugs came onto the market just as the QTc interval and TdP were beginning to attract attention; relevant findings about these drugs are, therefore, available from their approval studies, and much attention has been paid to their side effects. In contrast, for many older psychotropic drugs, all that is known about their influence on the QTc interval or on the risk of TdP is derived from reports of sudden cardiac death, without any more specific classification. For some drugs, in fact, there have been no relevant studies or reports at all (as indicated by "N.R." in the *Table*). Such is the case for opipramol and prothipendyl, two drugs that are sold only in Europe or in Germany. It cannot be concluded from the lack of relevant publications that these medications confer no risk of QTc prolongation or of TdP. When interpreting TdP case numbers, one must bear in mind the frequency with which different medications are prescribed (2); thus, the *Table* also contains data on the volume of drug prescriptions in Germany in the year 2009 (11).

Classic antipsychotic drugs

Thioridazine has been found to prolong the QTc interval to the greatest extent, followed by pimozide and haloperidol (12). The risk of pathological QTc prolongation rises with the dose. These three drugs are also known to confer a higher risk of TdP than other psychotropic drugs (5, 13). Thioridazine is therefore used only as a second-line antipsychotic drug (5). The low-potency antipsychotic drugs chlorpromazine and levomepromazine have only been reported to prolong the QTc interval when given in high doses (100 mg) (6). In general, however, the risk of TdP is much lower with antipsychotic drugs than with cardiac drugs (2).

An analysis of reported adverse effects of haloperidol, compiled by Johnson & Johnson, identified 229 cases of abnormally long QTc intervals, among which were 73 cases of TdP. Eleven (15%) of the TdP cases were fatal, and 8 (73%) of these deaths occurred after haloperidol had been given intravenously (12, 14, e1). In another study, TdP arose in 8 of 268 patients (3.6%) given haloperidol intravenously for sedation in an intensive care unit; 7 of them had received more than 35 mg of haloperidol (range: 9 to 400 mg) in a 24-hour period, and the incidence of TdP after high intravenous doses of haloperidol was calculated at 11% (15). In another retrospective study involving 37 patients over age 65 (80% of them women) who developed pathological QTc prolongation, TdP events, or sudden death while being treated with psychotropic drugs, intravenously administered haloperidol was the most commonly implicated drug, having been given in 38% of cases (16). In a cohort study of psychiatric intensive-care patients who were given haloperidol, 4.3% of the 375 patients given the drug by mouth had a pathological QTc interval (dose: 15.9 ± 12.6 mg), as did 17% of the 47 patients receiving it intravenously (dose: 16.0 ± 10.5 mg) (12). In summary, it can be concluded that high intravenous doses of haloperidol elevate the risk of TdP.

The United States Food and Drug Administration (FDA) recently warned of the risk of cardiac arrhythmias in connection with intravenously administered

TABLE

Effects of psychotropic drugs on QTc and the occurrence of torsade de pointes (TdP)

Drug	QTc prolongation	QTc (Bazett) prolongation compared to baseline in ms (n); reference no.	Reported cases of TdP	TdP risk (Arizona CERT)	DDD in Germany, 2009 (millions)	References
Typical high-potency antipsychotic drugs						
Thioridazine[1]	+++	+28 to 36.6 (n = 60); 10	+++	1	1.3	2, 4–6, 10, 12–14, 23, 24, e6
Haloperidol[1]	+	+3.8 to 8.9 (n = 147; 4–15 mg); 4	+++	1	18.4	2, 4–6, 8, 10, 12–15, 19, 23, 24, e1, e6
Pimozide[1]	+++	+19 to 24 (n = 97); 10	+	1	1.0	2, 5, 6, 10, 19, 23, 24, e29
Perphenazine[1]	+	-55 to -16.6 (-35.7; n = 4); 7	+		0.5	5, 7
Fluphenazine[1]	+		+		8.2	5–7, 24, 25
Flupentixole[1]	+		N.R.		9.6	5, 6, 25
Benperidol[1]	Ø	-17.1 (n = 1); 7	N.R.		9.0	7, 12
Bromperidol[1]	+	-15.6 to 19.2 (+1.8; n = 5); 7	N.R.		9.0	7, 12
Zuclopenthixole[1]	Ø	-25.5 to 1.1 (-12.2; n = 9); 7	N.R.		5.3	5, 7
Perazine[1]	N.R.		N.R.		15.2	
Fluspirilene	N.R.		N.R.		3.2	
Typical low-potency antipsychotic drugs						
Chlorpromazine[1]	++		++	1	N.R.	6, 12, 13, 23–25, e30, e31
Melperone[1]	+++	+30 (n = 23); e32	+		12.2	5, 24, e32
Levomepromazine[1]	++	-18 to 11.8 (-31; n = 6); 7	N.R.		3.8	5, 7, 12, e33
Promethazine[1]	+		+		32.4	e34
Pipamperone[1]	+	-10.8 to 9.6 (-0.6; n = 15); 7	+		9.3	2, 7, e35
Prothipendyl[1]	Ø		N.R.		3.3	5
Chlorprothixene[1]	Ø		N.R.		6.6	5
Newer antipsychotic drugs						
Ziprasidone[1]	++	+9.7 (n = 3095); 13	+++	2	5.3	2, 3, 13, 19, 23
Sertindole[1]	+++	+11 to 30 (n = 510); 10	+	2	N.R.	2, 10, 13, 14, 18, 23, 24
Quetiapine[1]	+++	-2 to +19.7 (n = 312); 10	++	2	33.3	2, 5, 10, 19, 23, 24, e36, e37
Risperidone[1]	++	+2 to 11.6 (n = 185); 10	+	2	29.0	2, 5, 6, 10, 14, 17, 19, 24, e3, e38
Clozapine	++	+10 (n = 13); 10	+	2	13.3	2, 5, 6, 10, 13, 23, 24, e6, e7
Paliperidone[1] ER	Ø	+1.7 to 3.7 (n = 1300); e4	N.R.	2	3.2	e4
Sulpiride[1]	++		+		4.1	5, 13, 24, e12, e13
Amisulpride[1]	+	-5.9 (n = 12); 13	++		7.0	2, 5, 13, 23, 24, e9, e39
Zotepine[1]	+	+8.3 (n = 537); 13	N.R.		0.8	5, 13, 23, e40
Olanzapine[1]	+	-4.5 to +8.4 (n = 1342); 10	N.R.		32.7	2, 5, 10, 13, 14, 23, 24, e10
Aripiprazole	Ø	-4 to -3.5 (n = 828); 10	N.R.		8.0	2, 10, 14, e11
Tri-and tetrayclic antidepressants						
Amitriptyline[1]	+++	+1 to 21 (n = 117); 10	++	3	94.5	7, 10, 18, 23, 24, e21, e23
Doxepine	+++	+8 to 22 (n = 20); 10	++	3	54.2	7, 10, 18, 23, 24, e24
Imipramine[1]	+++	+4 to 20 (n = 76); 10	+	3	2.6	7, 10, 23, 24, e25
Clomipramine[1]	++	-1.6 to 14.7 (+6,6; n = 19); 7	++	3	8.1	7, 10, 18, 23, 24
Desipramine[1]	+++	+11 to 24 (n = 74); 10	+	3	N.R.	10, 18, 23, 24
Nortriptyline[1]	+++	+7 to 30 (n = 129); 10	N.R.	3	2.5	7, 10, 23
Trimipramine[1]	Ø		N.R.	3	31.6	e41
Maprotiline	+++	+17 (n = 95); 10	++		3.8	7, 10, 18, 23, 24, e22, e42
Mirtazapine	+	+3.1 (n = 338); 9, 10	+		123.1	7, 10, 19

Drug	QTc prolongation	QTc (Bazett) prolongation compared to baseline in ms (n); reference no.	Reported cases of TdP	TdP risk (Arizona CERT)	DDD in Germany, 2009 (millions)	References
Trazodone[1]	+	-4 to +7 (n = 52); 10	+		2.0	10, 23, 24, e15, e16
Mianserine	+	-10.3 to 6.9 (-1,7; n = 20); 7	+		N.R.	7, 23
Opipramol	Ø		N.R.		74.0	e43
SSRI/SSNRI/SNRI[2]						
Venlafaxine[1]	+	+4.7 (n = 357); 10	+	2	75.1	7, 10, 14, 24, e44, e45
Citalopram[1]	+	-10 to 0 (n >900); 10	++	3	241.7	7, 8, 10, 14, 19, 20, e18–20
Fluoxetine	++	0 to 10 (n = 370); 10	++	3	43.3	8, 10, 19, 20, 23, 24
Paroxetine	Ø	-3.1 to 4.2 (+0.6; n = 111); 7	++	3	42.3	7, 10, 19, 20, 24
Sertraline	Ø	0 (n = 2500); 10	N.R.	3	55.1	7, 10
Escitalopram[1]	+		N.R.			17, 20
Fluvoxamine	Ø	0 to 2 (n = 99); 10	N.R.		N.R.	7, 10
Reboxetine	Ø		N.R.		6.8	e46
Duloxetine	Ø		N.R.		34.7	e47–50
Other antidepressants						
Lithium[1]	+++	0.7 to 19.4 (+10.1; n = 18); 7	N.R.	2	20.3	6, 7, 12, 14, 24, e16
Bupropion	+	-6.4 to -0.3 (n = 80); 10	+		6.5	7, 10, 23, 24
Buspirone	N.R.		N.R.		1.0	
Hypericum	Ø	-5 (n = 84); 10	N.R.		27.7	10
Moclobemide	Ø	-0.3 (n = 3); 7	N.R.		N.R.	7
Tranylcypromine	Ø	+4 (n = 10); 10	N.R.		2.7	7, 10, 24
Sedatives and other psychotropic drugs						
Methadone[1]	+++	17 ± 5 (n = 55); 22	+++	1	2.8	22, 24, e26–28, e51
Levomethadone[1]	+++	27 ± 4.5 (n = 55); 22	+	1	5.4	22, 24, e51
Chloral hydrate[1]	+		+	2	1.8	23, 24, e52
Methylphenidate	Ø		N.R.	3	55.3	e53, e54
Atomoxetine[1]	Ø		N.R.	3	2.6	e55, e56
Tiapride[1]	+		+		5.0	2, 23, 24
Carbamazepine	Ø		N.R.		53.9	6, 12, e57–e59
Valproate	Ø		N.R.		53.1	12, 24, e60
Lamotrigine	Ø		N.R.		20.2	e59, e61
Biperidene	Ø		N.R.		9.9	12
Diazepam	Ø		N.R.		31.0	12

[1] The summary of product characteristics (SPC) warns of QTc prolongation/TdP, esp. with overdose in combination with other QTc-prolonging drugs or in case of hypokalemia.
[2] Selective serotonin-reuptake in hibitors(SSRI), selective norepinephrine-reuptake inhibitors (SNRI), selective serotonin/norepionephrine-reuptake inhibitors (SSNRI).

QTc prolongation::
Ø, none at therapeutic concentrations;
+, mild (>5 and <9 ms) or only in case of overdose or intoxication;
++, moderate (≥9 and <16 ms);
+++, severe (≥17 ms);
ER, extended-release formulation;
n, number of study participants.

Reported cases of TdP:
N.R., not reported;
+, rare cases in combination with other drugs that elevate the risk of TdP, or in the setting of overdose or intoxication;
++, rare cases under monotherapy and/or at therapeutic concentrations;
+++, multiple case reports or studies.

TdP risk according to the Arizona CERT (9):
1, generally accepted elevated risk of TdP;
2, rare case reports of TdP, possible but not adequately documented TdP risk;
3, weak association with TdP, unlikely at therapeutic doses, elevated TdP risk in the presence of congenital QT syndrome.

DDD, number of defined daily doses in Germany (11).

haloperidol (e1). Moreover, the summary of product characteristics (SPC) of haloperidol solution for injection has been changed to include a notice that it should only be given intramuscularly, not intravenously. In cases where (off-label) intravenous administration is judged to be clinically necessary, this should be done only under continuous ECG monitoring for the detection of QT prolongation and severe cardiac arrhythmias (e2).

Newer antipsychotic drugs

Among the newer antipsychotic drugs, sertindole and ziprasidone prolong the QTc to the most marked extent. The frequency of QTc intervals of 500 ms or longer is 3.1% to 7.8% with sertindole and 0.06% with ziprasidone (13). Moderate QTc prolongation is sometimes seen under treatment with risperidone even at therapeutic doses, mainly in older patients. Slow CYP2D6 metabolizers and patients concomitantly taking other drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, bupropion, and duloxetine, are at particularly elevated risk (e3). Clinical studies of paliperidone revealed moderate QTc prolongation, which was much less severe when the extended release preparation was used (e4). In clinical approval studies, quetiapine was found to be associated with only mild prolongation of the QTc interval, and clozapine with none at all (e5, e6). In a retrospective study, 2 of 61 patients treated with clozapine had QTc intervals of 500 ms or longer (e7). It should be borne in mind, however, that clozapine can cause myocarditis and thus sensitize patients to the QTc-prolonging effect of other drugs (e8).

A retrospective study of cases of amisulpride intoxication revealed a very high rate of pathological QTc prolongation (73% of 83 patients, doses ranging from 4 to 80 mg) and a 7% rate of TdP events (13, e9). Olanzapine and zotepine were also found to prolong the QTc interval to a pathological extent only when given in excessive doses (13, e10). Aripiprazole has not yet been reported to have caused even a single case of QTc prolongation (e11).

A prospective study involving female patients with schizophrenia revealed that the combination of an antipsychotic drug (haloperidol, clozapine, risperidone, or olanzapine) with other antipsychotic drugs or antidepressants (SSRI, mirtazapine, venlafaxine, or clomipramine) prolonged the QTc interval by 24 ± 21 ms, while monotherapy with an antipsychotic drug did not prolong it at all (change, – 1 ± 30 ms) (17).

An analysis of 1665 spontaneous reports of TdP cases to the FDA's Adverse Event Reporting System (AERS) (2004–2007) revealed that the antipsychotic drugs most commonly associated with TdP were ziprasidone (28 cases), haloperidol (18), risperidone (19), and quetiapine (14). This analysis unfortunately took no account of concomitantly taken medications, or of drugs for which fewer than 10 cases of TdP were reported (19). Nonetheless, one can conclude from these figures that ziprasidone, which is much less commonly prescribed than the other three drugs mentioned, is clearly associated with a higher risk of TdP than any of them.

There have been only two reported cases of TdP under treatment with clozapine; in both, clozapine was given in combination with another drug that can prolong the QTc (pimozide in one case, clonazepam in the other) (2, e6). With regard to sulpiride, one case of TdP has been reported at a therapeutic dose (e12) and one with an intoxication (e13); two TdP cases have been reported in association with sertindole intoxication (13). TdP has not been reported to date in association with olanzapine, aripiprazole, or zotepine (14). It thus seems that olanzapine, a commonly prescribed antipsychotic drug, is unlikely to cause TdP. It should not be forgotten, however, that QTc prolongation is more common, and the risk of TdP is higher, when antipsychotic drugs and other psychotropic drugs are given in combination (e14).

Antidepressants

While imipramine, amitriptyline, nortriptyline, desipramine, maprotiline, and doxepine can markedly prolong the QTc, clinical studies have revealed no more than mild QTc prolongation with the use of clomipramine, mirtazapine, and trazodone (10, 14), and mainly in overdoses in the case of trazodone (e15, e16). In the approval studies for the selective monoamine reuptake inhibitors (SSRIs, venlafaxine, duloxetine, reboxetine), therapeutic doses of these drugs were not found to have any effect on the QTc interval. Nonetheless, case reports published after drug approval and analysis of toxicological databases have revealed that QTc prolongation can arise under treatment with fluoxetine, citalopram, or venlafaxine at toxic doses, or when multiple additional risk factors are present (10, 14, 20). Lithium in concentrations above 1.2 mmol/L can markedly prolong the QTc interval (e17).

Among the cases of TdP that were spontaneously reported to the AERS of the FDA from 2004 to 2007, the most commonly implicated antidepressants were citalopram (12 cases), fluoxetine (12), paroxetine (11), and mirtazapine (10); these, however, were also the most commonly prescribed antidepressants during the same period (19). Among the 88 cases of TdP reported from 1991 to 2006 to the Swedish Drug Information System (SWEDIS), a spontaneous registry system, there were, surprisingly, 9 cases (10%) under therapeutic doses of citalopram (sold in Sweden from 1998 onward); in 5 of these cases, citalopram was the only drug that could have been responsible for TdP (8). Further invididual case reports of TdP under treatment with citalopram (21, e18–e20), fluoxetine, paroxetine (20), and TCAs (18, e21–e25) have been published, but always in the setting of additional risk factors, intoxication, or combination with other drugs known to raise the risk of TdP. Even though the number of published case reports admittedly cannot yield an adequate estimate of the risk of TdP, and even though there is a bias towards newer agents such as citalopram in the reporting of adverse reactions, one can at least conclude that treatment with

SSRIs, particularly citalopram, fluoxetine, and paroxetine, can cause TdP when additional risk factors are present, or when these drugs are given at excessive doses.

Other psychotropic drugs

Methadone can prolong the QTc in dose-dependent manner, sometimes as markedly as sotalol does, particularly when protein binding of the drug is low, as in malnourished cancer patients and narcotic addicts (e26, e27). A randomized, double-blind trial involving 154 opioid-dependent patients whose QTc intervals were initially normal revealed that the QTc can be pathologically prolonged even when methadone is given as its R-enantiomer (levomethadone), as is now most commonly done in Germany: 28% of the patients receiving levomethadone and 23% of those receiving methadone developed QTc intervals longer than 470 ms (22). Methadone was among the drugs most commonly associated with TdP events reported to the AERS, accounting for 83 cases (19). An analysis of 40 cases of TdP in patients receiving methadone substitution revealed that additional risk factors were present in most cases, including high doses of methadone, concomitant medication interfering with methadone metabolism or elevating the risk of TdP, HIV infection, hypokalemia, hepatic cirrhosis, renal failure, and heart disease (e28).

Treatment recommendations

Clearly, in clinical practice, the use of psychotropic drugs that affect myocardial repolarization cannot be entirely avoided. Nonetheless, every attempt should be made to avoid the combined use of multiple drugs that can prolong the QTc interval and elevate the risk of TdP. Furthermore, the individual risk in each patient should be carefully considered, and any additional risk factors should be minimized. The following precautions are recommended (2, 5):

- ECG recording before treatment is begun and under steady-state conditions afterward,
- slow dose escalation and adaptation of the dose in case of altered elimination or concurrent medication sharing the same metabolic pathway,
- regular ECG monitoring of patients at high risk and those taking additional medications that can prolong the QTc interval,
- monitoring of the serum potassium concentration (which should be kept in the high normal range in patients at high risk),
- careful attention to potential electrolyte loss caused by diarrhea, vomiting, profuse sweating, undernourishment, diuretic therapy, alcohol and/or drug use, and eating disorders,
- administration of magnesium sulfate (orally or intravenously) if the QTc interval is markedly prolonged,
- discontinuation of medication if the QTc is longer than 500 ms, the potassium concentration is normal, and the QRS is of normal duration, even if the patient has no symptoms, and
- consideration of cardiac arrhythmia as a possible cause of every newly presenting case of palpitations, dizziness, syncope, or convulsions.

KEY MESSAGES

- Many antipsychotic and antidepressant drugs are known to prolong the QTc interval in a dose-dependent manner. Nonetheless, because torsade de pointes (TdP) is a rare tachyarrhythmia, there are only rare case reports of TdP in association with most psychotropic drugs, and the risk of TdP therefore cannot be precisely estimated.
- Haloperidol markedly elevates the risk of TdP, mainly when high doses (>35 mg/d) are given intravenously; in one study, the observed probability of TdP under these circumstances was 11%.
- Multiple psychoactive drugs that prolong the QTc only mildly or not at all when used individually can prolong it to a pathological extent and cause TdP when given in combination.
- Most published cases of TdP associated with psychotropic drugs involved additional risk factors such as heart disease, age over 65 years, female sex, and/or hypokalemia.
- When psychotropic drugs that elevate the risk of TdP are prescribed, regular monitoring of the ECG and the serum electrolytes is recommended, particularly for patients at high risk. The serum potassium concentration should lie in the high normal range.

Conflict of interest statement

Dr. Wenzel-Seifert states that she has no conflict of interest.

Dr. Wittmann has lectured for AstraZeneca, GlaxoSmithKline, Lilly, Pfizer, and Eisai. He has received consultant's fees from Bristol-Myers Squibb and payment for publications from Servier and has been a physician investigator in clinical pharmacological trials for Servier, AstraZeneca, Janssen-Cilag, Pfizer, and Lilly.

Prof. Dr. Haen states that he has given lectures, served on scientific advisory boards, and served as a physician investigator in clinical trials for Janssen-Cilag, Lilly, Pfizer, GlaxoSmithKline, AstraZeneca, Bristol-Myers Squibb, Otsuka, Bayer Vital, Servier, and Südmedica GmbH.

Manuscript submitted on 13 September 2010, revised version accepted on 10 March 2011.

REFERENCES

1. Altmann D, Eggmann U, Ammann P: Medikamentös induzierte Verlängerung des QT-Intervalls. [Drug induced QT prolongation]. Wien Klin Wochenschr 2008; 120: 128–35.
2. Haverkamp H, Deuschle M: Antipsychotikainduzierte QT-Verlängerung. [Antipsychotica-induced QT-prolongation]. Nervenarzt 2006; 77: 276–88.
3. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohmann RG: Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007; 153: 891–9.
4. Harrigan EP, Miceli JJ, Anziano R, Watsky E, Reeves KR, Cutler NR, et al.: A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacology 2004; 24: 62–9.
5. Stöllberger C, Huber JO, Finsterer J: Antipsychotic drugs and QT prolongation. Int Clin Psychopharmacology 2005; 20: 243–51.
6. Reilly JG, Ayes SA, Ferrier IN: QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 335: 1048–52.
7. van Noord C, Straus S, Sturkenboom M, Hofman A, Aarnoudse AJ, Bagnardi V, et al.: Psychotropic drugs associated with corrected QT interval prolongation. J Clin Psychopharmacology 2009; 29: 9–15.

8. Astrom-Lilja C, Odeberg JM, Ekman E, Hägg S: Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. Pharmacoepidemiology and Drug Safety 2008; 17: 587–92.
9. Woosley RL, Anthony M, Armstrong EP, Assenzo JR for Arizona CERT – QT Drug Lists by Risk Groups: accessed 30. 8. 2010, http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.
10. Goodnick PJ, Jerry J, Parra F: Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother 2002; 3: 479–98.
11. Lohse MJ, Müller-Oerlinghausen B: Psychopharmaka. In: Schwabe U, Paffrath D (eds.): Arzneiverordnungs-Report 2010: Aktuelle Daten, Kosten, Trends und Kommentare. Berlin 2010: 497–841.
12. Ozeki Y, Fujii K, Kurimoto N, Yamada N, Okawa M, Aoki T, et al.: QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 401–5.
13. Haddad PM, Anderson IM: Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002; 62: 1649–71.
14. Alvarez PA, Pahissa J: QT alterations in psychopharmacology: proven candidates and suspects. Curr Drug Saf 2010; 5: 97–104.
15. Sharma ND, Rosmann HS, Padhi ID, Tisdale JE: Torsades de pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998; 81: 238–40.
16. Vieweg WV, Wood MA, Fernandez A, Beatty-Brooks M, Hasnain M, Pandurangi AK: Proarrhythmic risk with antipsychotic and antidepressant drugs: implications in the elderly. Drugs Aging 2009; 26: 997–1012.
17. Sala M, Vicentini A, Brambilla P, Montomoli C, Jogia JR, Caverzasi E, et al.: QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. Ann Gen Psychiatry 2005; 4(1): 1. doi: 10.1186/744–859X-4–1.
18. Vieweg WV, Wood MA: Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. Psychosomatics 2004; 45: 371–7.
19. Poluzzi E, Raschi E, Moretti U, De Ponti F: Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 2009; 18: 512–8.
20. Wenzel-Seifert K, Wittmann M, Haen E: Torsade de Pointes episodes under treatment with selective serotonin reuptake inhibitors. Pharmacopsychiatry 2010; 43: 279–81.
21. de Gregorio C, Morabito G, Cerrito M, Dattilo G, Oreto G: Citalopram-induced long QT syndrome and torsade de pointes: Role for committant therapies and illnesses. Int J Cardiol 2011; 148: 226–8.
22. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC: QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med 2007; 167: 2469–75.
23. DePonti F, Poluzzi E, Montanaro N: Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. Eur J Clin Pharmacol 2001; 57: 185–209.
24. Haverkamp W, Haverkamp F, Breithard G: Medikamenteninduzierte QT-Verlängerung und Torsade de pointes. Ein multidisziplinäres Problem. Dtsch Ärztebl 2002; 99: A 1872–9.
25. Chong SA, Mythily, Lum A, Goh HY, Chan YH: Prolonged QTc intervals in medicated patients with schizophrenia. Hum Psychopharmacol 2003; 18: 647–9.

Corresponding author
Dr. med. Katharina Wenzel-Seifert
Klinische Pharmakologie, Klinik und Poliklinik für Psychiatrie, Psychosomatik und Psychotherapie der Universität Regensburg
Universitätstr. 84
93053 Regensburg, Germany
Wenzel-Seifert.Katharina@klinik.uni-regensburg.de

For eReferences please refer to:
www.aerzteblatt-international.de/ref4111

REVIEW ARTICLE

QTc Prolongation by Psychotropic Drugs and the Risk of Torsade de Pointes

by Katharina Wenzel-Seifert, Markus Wittmann, and Ekkehard Haen

eReferences

e1. FDA: Information for Healthcare Professionals: Haloperidol. FDA ALERT 9/2007, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085203.htm

e2. Arzneimittelkommission der Deutschen Ärzteschaft: Information über die Änderung der bisher empfohlenen Applikationswege von Haldol®-Janssen-Injektionslösung. AkdÄ Drug Safety Mail 2010–098 5th May 2010, http://www.akdae.de/Arzneimittelsicherheit/DSM/Archiv/2010–098.html

e3. Llerena A, Berecz R, Dorado P, de la Rubia A: QTc interval, CYP2D6 and CYP2C9 genotypes and risperidone plasma concentrations. J Psychopharmacol 2004; 18: 189–93.

e4. Janicak PG, Winans EA: Paliperidone ER: a review of the clinical trial data. Neuropsychiatr Dis Treat 2007; 3: 869–97.

e5. Lieberman JA, Strout TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al.: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353: 1209–23.

e6. Warner B, Hoffmann P: Investigation of the potential of clozapine to cause torsade de pointes. Adverse Drug React Toxicol Rev 2002; 21: 189–203.

e7. Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo YJ, et al.: Electrocardiographic abnormalities in patients treated with clozapine. J Clin Psychiatry 2000; 61: 441–6.

e8. Llorca PM, Pere JJ: Leponex®, 10 ans après – Une revue clinique [Leponex, 10 years after -- a clinical review] [Article in French]. Encephale 2004; 30: 474–91.

e9. Isbister GK, Balit CR, MacLoed D, Duffull SB: Amisulpride overdose is frequently associated with QT prolongation and torsades de pointes. J Clin Psychopharmacol 2010; 30: 391–5.

e10. Brugisser M, Bravo A, Bodner M: Medikamenten-assoziiertes Long-QT-Syndrom [Medication associated long QT syndrome]. Praxis 2009; 98: 1409–15.

e11. Goodnick PJ, Jerry JM: Aripiprazole: profile on efficacy and safety. Expert Opin Pharmacother 2002; 3: 1773–81.

e12. Huang BH, Hsia CP, Chen CY: Sulpiride induced torsade de pointes. Int J Cardiol 2007; 118: e100–2.

e13. Chang JH, Weng TI, Fang CC: Long QT syndrome and torsades de pointes induced by acute sulpiride poisoning. Am J Emerg Med 2009; 27: 1016. e1–3

e14. Sala M, Vicentini A, Brambilla P, Montomoli C, Jogia JR, Caverzasi E, et al.: QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. Ann Gen Psychiatry 2005; 4: 1–6.

e15. Dattilo PB, Nordin C: Prolonged QT associated with an overdose of trazodone. J Clin Psychiatry 2007; 68: 1309–10.

e16. Levenson JL: Prolonged QT interval after trazodone overdose. Am J Psychiatry 1999; 156: 969–70.

e17. Hsu CH, Liu PY, Chen JH, Yeh TL, Tsai HY, Lin LJ: Electrocardiographic abnormalities as predictors for over-range lithium levels. Cardiology 2005; 103: 101–6.

e18. Kanjanauthai S, Kanluen T, Charreonthaitawee P: Citalopram induced torsade de pointes, a rare life threatening side effect. Intl J Cardiol 2008; 131: e33–e34.

e19. Meuleman C, Jourdain P, Bellorini M, Sadeg N, Loiret J, Guillard N, et al.: Citalopram et torsades de pointes : A propos d'un cas. [Citalopram and Torsades de Pointes: A case report]. Archives des maladies du coeur et des vaisseaux 2001; 94: 1021–4.

e20. Tarabar AF, Hoffman RS, Nelson L: Citalopram overdose: late presentation of torsades de pointes (TdP) with cardiac arrest. J Med Toxicol 2008; 4: 101–5.

e21. Dorsey ST, Biblo LA: Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. Am J Emerg Med 2000; 18: 227–9.

e22. Lentini S, Rao ML, Schröder R, Lüderitz B, Bauriedel G: QT-Verlängerung und Torsade de pointes-Tachykardie bei Therapie mit Maprotilin. Differenzialdiagnostische und -therapeutische Aspekte. [QT prolongation and torsade de pointes tachycardia during therapy with maprotiline. Differential diagnostic and therapeutic aspects]. Dtsch Med Wochenschr 2001; 49: 1396–400.

e23. Davison ET: Amitriptyline-induced Torsade de Pointes. Successful therapy with atrial pacing. J Electrocardiol 1985; 18: 299–301.

e24. Alter P, Tontsch D, Grimm W: Doxepin-induced torsade de pointes tachycardia. Ann Intern Med 2001; 135: 384–5.

e25. Tzivoni D, Keren A, Cohen AM, Loebel H, Zahavi I, Chenzbraun A, et al.: Magnesium therapy for torsades de pointes. Am J Cardiol 1984; 53: 528–30.

e26. Reddy S, Hui D, El Osta B, de la Cruz M, Walker P, Palmer JL, et al.: The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study. J Palliat Med 2010; 13: 33–8.

e27. George S, Moreira K, Fapohunda M: Methadone and the heart: what the clinician needs to know. Curr Drug Abuse Rev 2008; 1: 297–302.

e28. Justo D, Gal-Oz A, Paran Y, Goldin Y, Zeltser D: Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. Addiction 2006; 101: 1333–8.

e29. Krähenbühl S, Sauter B, Kupferschmidt H, Krause M, Wyss PA, Meier PJ: Case report: reversible QT prolongation with torsades de pointes in a patient with pimozide intoxication. Am J Med Sci 1995; 309: 315–6.

e30. Hoehns JD, Stanford RH, Geraets DR, Skelly KS, Lee HC, Gaul BL: Torsades de pointes associated with chlorpromazine: case report and review of associated ventricular arrhythmias. Pharmacotherapy 2001; 21: 871–83.

e31. Ochiai H, Kashiwagi M, Usui T, Oyama Y, Tokita Y, Ishikawa T: [Torsade de Pointes with T wave alternans in a patient receiving moderate dose of chlorpromazine: report of a case] Japanese. Kokyu To Junkan 1990; 38: 819–22.

e32. Hui WK, Mitchell LB, Kavanagh KM, Gillis AM, Wyse DG, Manyari DE, et al.: Melperone: electrophysiologic and antiarrhythmic activity in humans. J Cardiovasc Pharmacol 1990; 15: 144–9.

e33. Kondou N, Hiasa Y, Kishi K, Fujinaga H, Ohishi Y, Ohtani R, et al.: [A case of life-threatening ventricular arrhythmias probably due to psychotropic drugs]. [Article in Japanese]. Kokyu To Junkan 1993; 41: 1117–20.

e34. Jo SH, Hong HK, Chong SH, Lee HS, Choe H: H1 antihistamine drug promethazine directly blocks hERG K+ channel. Pharmacol Res 2009; 60: 429–37.

e35. Bont L, Bosker HA, Brus F, Yska JP, Bosch FH: Torsade de pointes after pipamperone intoxication. Pharm World Sci 1998; 20: 137.

e36. Vieweg WV, Schneider RK, Wood MA: Torsade de pointes in a patient with complex medical and psychiatric conditions receiving low-dose quetiapine. Acta Psychiatr Scand 2005; 112: 318–20.

e37. Gajwani P, Pozuelo L, Tesar GE: QT interval prolongation associated with quetiapine (Seroquel) overdose. Psychosomatics 2000; 41: 63–5.

e38. Blaschke D, Parwani AS, Huemer M, Rolf S, Boldt LH, Dietz R, et al.: Torsade de pointes during combined treatment with risperidone and citalopram. Pharmacopsychiatry 2007; 40: 294–5.

e39. Chung AKK, Chua SE: Torsade de pointes with low-dose amisulpride: a case report. J Psychopharmacol 2010; 24: 433–5.

e40. Lin YC, Su HK, Ouyang WC, Lane HY: Zotepine-induced QTc prolongation. J Clin Psychopharmacol 2008; 28: 576–8.

e41. Cohn JB, Wilcox CS, Goodman LI: Antidepressant efficacy and cardiac safety of trimipramine in patients with mild heart disease. Clin Ther 1992; 15: 115–26.

e42. Züchner H: QT-Verlängerung und Torsade de pointes-Tachykardie bei Therapie mit Maprotilin. [QT prolongation and torsade de pointes-tachycardia in therapy with maprotiline]. Dtsch Med Wochenschr 2002; 127: 983–4.

e43. Möller HJ, Volz HP, Reimann IW, Stoll KD: Opipramol for the treatment of generalized anxiety disorder: a placebo-controlled trial including an alprazolam-treated group. J Clin Psychopharmacol 2001; 21: 59–65.

e44. Letsas K, Korantzopoulos P, Pappas L, Evangelou D, Efremidis M, Kardaras F: QT interval prolongation associated with venlafaxine administration. Int J Cardiol 2006; 109: 116–7.

e45. Bosse GM, Spiller HA, Collins AM: A fatal case of venlafaxine overdose. J Med Toxicol 2008; 4: 18–20.

e46. Fleishaker JC, Francom SF, Herman BD, Knuth DW, Azie NE: Lack of effect of reboxetine on cardiac repolarization. Clin Pharmacol Ther 2001; 70: 261–9.

e47. Norman TR, Olver JS: Duloxetine in the treatment of generalized anxiety disorder. Neuropsychiatr Dis Treat 2008; 4: 1169–80.

e48. Raskin J, Wiltse CG, Dinkel JJ, Walker DJ, Desaiah D, Katona C: Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. J Clin Psychopharmacol 2008; 28: 32–8.

e49. Wernicke J, Lledó A, Raskin J, Kajdasz DK, Wang F: An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug Saf 2007; 30: 437–55.

e50. Zhang L, Chappell J, Gonzales CR, Small D, Knadler MP, Callaghan JT, et al.: QT effects of duloxetine at supratherapeutic doses: a placebo and positive controlled study. J Cardiovasc Pharmacol 2007; 49: 143–53.

e51. Ansermont N, Albayrak O, Schläpfer J, Crettol S, Croquette-Krokar M, Bourquin M, et al.: Substitution of (R,S)-methadone by (R)-methadone: Impact on QTc interval. Arch Intern Med 2010; 170: 529–36.

e52. Sing K, Erickson T, Amitai Y, Hryhorczuk D: Chloral hydrate toxicity from oral and intravenous administration. J Toxicol Clin Toxicol 1996; 34: 101–6.

e53. Hill SL, El-Khayat RH, Sandilands EA, Thomas SH: Electrocardiographic effects of methylphenidate overdose. Clin Toxicol (Phila) 2010; 48: 342–6.

e54. Negrao BL, Crafford D, Viljoen M: The effect of sympathomimetic medication on cardiovascular functioning of children with attention-deficit/hyperactivity disorder. Cardiovasc J Afr 2009; 20: 296–9.

e55. Simpson D, Plosker GL: Spotlight on atomoxetine in adults with attention-deficit hyperactivity disorder. CNS Drugs 2004; 18: 397–401.

e56. Wernicke JF, Faries D, Girod D, Brown J, Gao H, Kelsey D, et al.: Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug Saf 2003; 26: 729–40.

e57. Ciszowski K, Szpak D, Jenner B: The influence of carbamazepine plasma level on blood pressure and some ECG parameters in patients with acute intoxication. Przegl Lek 2007; 64: 248–51.

e58. Kwon S, Lee S, Hyun M, et al.: The potential for QT prolongation by antiepileptic drugs in children. Pediatr Neurol 2004; 30: 99–101.

e59. Saetre E, Abdelnoor M, Amlie J, Tossebro M, Perucca E, Taubøll E, et al.: Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine. Epilepsia 2009; 50: 1841–9.

e60. Kurt E, Emul M, Ozbulut O, Guler O, Erdur F, Sağlam H, et al.: Is valproate promising in cardiac fatal arrhythmias? Comparison of P- and Q-wave dispersion in bipolar affective patients on valproate or lithium-valproate maintenance therapy with healthy controls. J Psychopharmacol 2009; 23: 328–33.

e61. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, et al.: Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. Br J Clin Pharmacol 2008; 66: 396–404.