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Psychoactive Drugs and Prolongation of the QT Interval

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Summary

The links between psychiatry and cardiology that are pertinent to potential cardiovascular risks associated with the use of psychotropic drugs, especially antipsychotics, cannot be viewed as entirely new. In Italy, however, an important innovation was made when, on 28 February 2007, the Italian Medicines Agency (AIFA), issued a directive laying down provisions for the amendment of the printed papers that accompany various medicines, including haloperidol; that initiative has revived the relevance of the whole question. In particular, contraindications to the use of these drugs have been redefined. The primary ones are now listed as acute myocardial infarction, decompensated heart failure, arrhythmias treated with antiarrhythmic drugs belonging to special classes, the prolongation of the QT interval corrected for heart rate (QTc), the family history for arrhythmia or torsades de pointes, hypokalaemia and the concomitant use of drugs that prolong the QTc.

Key Words: Psychoactive drugs; QT Interval prolongation

In 1992 the Food and Drug Administration (FDA), the US Government Agency responsible for regulating and supervising the safety of foods and pharmaceutical products, made a request to the manufacturers of a terfenadine-based antihistamine to “warn” physicians that in some patients administration of that drug could lead to the onset of life-threatening cardiac arrhythmias. Five years later, in 1997, the FDA considered whether it should withdraw terfenadine from the market and, in the following year, 1998, two multinational drug companies, on their own initiative, decided to take all the products containing terfenadine off the market.

Similar events have happened with other drugs, including the effective prokinetic drug cisapride and the promising antipsychotic sertindole. These two compounds had likewise been implicated by the FDA in the potential onset of electrocardiographic alterations, especially prolongation of the QT interval, also known as “long QT”. A prolonged QT interval is sometimes associated with a specific form of ventricular arrhythmia, torsades de pointes (TdP) which, although it is often resolved spontaneously, may result in sudden cardiac death.

As to sertindole, the FDA presented evidence of an

association between the use of this antipsychotic drug and the lengthening of the QT interval, resulting in torsades de pointes and sudden cardiac death. In a clinical trial comprising over 2,000 patients, 27 deaths had been registered, of which 16 were caused by adverse cardiac events. A review carried out by an independent panel of experts later reported that no patients had experienced torsades de pointes, concluding that sertindole was not implicated in any of the 27 deaths. Furthermore, the authors of that review demonstrated that, at the time of enrolment in the trials, many of those patients had already been diagnosed with cardiac disorders, while pointing out the frequency of sudden cardiac death in schizophrenic patients. In spite of these findings, in 1998 the British Committee in Safety of Medicine, after it had previously authorized use of the drug, gathered new evidence on a potential association between sertindole administration and the onset of malignant arrhythmias, leading the drug manufacturers to take sertindole off the market.

In Italy, a directive issued by the Italian Medicines Agency (AIFA) on February 28th 2007, providing for the amendment of information sheets on various medicinal specialities, some of which had a history of long-stand-

ing, widespread use, such as chlorpromazine, haloperidol and sulpiride, once again brought to the fore the problem of the lengthening of the QT interval and its clinical importance.

1. Long QT and torsades de pointes

The QT interval, measured from the start of the QRS complex to the end of the T wave, is the time required for ventricular depolarization followed by repolarization. These two phases take up shorter intervals as heart rate rises, and a precise measurement can only be obtained after correcting the QT interval to take account of the heart rate (corrected QT or "QTc").

Over the last decade numerous definitions of long QTc have been published; pathological peak values of 450 msec both for adult males and adult females were unanimously agreed on only recently. Values of over 500 msec are considered a marker of increased risk of torsades de pointes and sudden cardiac death.

Torsades de pointes is a differentiated, polymorphic form of ventricular tachycardia named in recognition of the distinctive pattern taken by the ECG recording when peaks in the QRS complex seem to revolve around the isoelectric line; the high frequency of ventricular activation associated with this form of arrhythmia induces a marked decrease in cardiac load and arterial pressure. This arrhythmia may degenerate into ventricular fibrillation leading to sudden cardiac death. When there are specific predisposing factors, women appear to run a higher risk than men of developing TdP [3].

An especially high risk of torsades de pointes is run by patients featuring an ECG finding of a prolonged QT interval correlated to a congenital long QT syndrome (including the Romano Ward Syndrome and Jeville-Lange-Nielson Syndrome), electrolyte imbalance (hypopotassiemia, hypocalcaemia, hypomagnesiemia), as well as the administration of drugs such as phenothiazine, tricyclic antidepressants, macrolid antibiotics and several antihistamines (terfenadine, astemizole). Any failure to diagnose and adequately treat torsades de pointes may result in the onset of asphygmic ventricular tachycardia or ventricular fibrillation [24].

From a clinical standpoint torsades de pointes is invariably expressed through specific signs and symptoms, including vertigo, palpitations, fainting and syncope, leading to sudden cardiac death. Patients undergoing treatment with drugs potentially capable of inducing arrhythmias should therefore be carefully monitored for the onset of any signs or symptoms, to be duly correlated with the duration of arrhythmia (an episode lasting only a few seconds may only cause a slight vertigo, whereas a persistent episode may result in death).

The treatment of torsades de pointes implies withdrawal of the drug associated with the onset of symptoms, correction of electrolyte imbalance and acid-base equilibrium, the introduction of intravenous magnesium therapy

and temporary implant of a high frequency pacemaker to shorten the QT interval.

Fortunately, drug-induced torsades de pointes is not a common event, even if it is potentially life-threatening, and is closely correlated with duration of the QT interval (the longer the QT interval, the higher the probability of onset of torsades de pointes). The unforeseeable and probably idiosyncratic onset of this proarrhythmia suggests an underlying interindividual genetic variability of heart cell response to various drugs [20].

The action potential is given by the influx of sodium and calcium ionic currents, repolarizing potassium currents. Alterations to or a blockade of these currents induce a lengthening of the action potential, subsequently recorded on the ECG as a prolongation of the QT interval.

After performing a risk assessment, the influence of other predisposing factors should be taken into account (naturally, in addition to a family history of sudden death or syncope during childhood or early adulthood, particularly if correlated with physical exertion or emotional factors): old age, female gender, systolic dysfunction of the left ventricle, ischaemic heart disease, bradycardia, alteration of electrolyte balance (particularly hypokalaemia and hypomagnesiemia), alteration of renal and hepatic functions, and so on.

Moreover, pharmacodynamic interactions, such as those coming into play with the concomitant administration of multiple drugs potentially capable of prolonging the QT interval (e.g. class I and class III antiarrhythmic drugs), and pharmacokinetic interactions triggered by the concomitant administration of inhibitors and/or inducers of drug metabolizing isoenzymes belonging to the CYP450 complex (e.g. ketoconazole, grapefruit juice and cigarette smoking) should be carefully evaluated [1].

When prescribing a drug potentially capable of prolonging the QT interval, both the therapeutic role of the drug (effective need for the drug, and availability of equally effective alternative pharmacological treatments featuring a better safety profile), and patients' conditions should be carefully considered. It should, in any case, be stressed that in a population with a negative history and without any predisposing risk factors, an indiscriminate use of ECG prior to initiating treatment with a drug potentially capable of prolonging the QT interval is unjustified, in view of the fact that failure to detect ECG abnormalities does not rule out the presence of a masked predisposition. Lastly, it should be borne in mind that in patients undergoing treatment with drugs potentially capable of prolonging the QT interval, ECG measurement of the latter (or rather measurement of QTc) should be performed at peak plasma concentrations of the drug, taking into due consideration the concomitant administration (when present) of other drugs that interfere with the QT interval.

A list of drugs potentially capable of prolonging the QT interval is available on the website of the Center for Research on Therapeutics University of Arizona (<http://>

Table 1. Drugs and Torsades de Pointes (TdP)

Drugs associated with risk of TdP	Drugs potentially associated with risk of TdP	Drugs that should be avoided in patients with LQTS (long QT syndrome)
Drugs that regulatory authorities generally consider capable of increasing the risk of TdP	Drugs which, according to some reports, are associated with TdP but for which there is no clear evidence of correlation with an increased risk of TdP	Drugs to be avoided in patients diagnosed with suspected or has been diagnosed with congenital LQTS
Haloperidol Amiodarone * Quinidine * Cisapride Chloroquine Chlorpromazine Clarithromycin Disopyramide * Domperidone Droperidol Erythromycin * Methadone * Pentamidine * Pimozide* Procainamide Sotalol * Terfenadine Thioridazine	Alfuzosin Amantadine Atazanavir Azithromycin Chloral hydrate Clozapine Felbamate Indapamide Levofloxacin Lithium Moxifloxacin Nicardipine Ofloxacin Ondansetron Paliperidone Quetiapine Risperidone Salmeterol Tamoxifen Venlafaxine Voriconazole Ziprasidone	Amitriptyline Quinidine * Ciprofloxacin Citalopram Clomipramine Cocaine Desipramine Dopamine Doxepin Fluconazole Fluoxetine Galantamine Imipramine Itraconazole Ketoconazole Nortriptyline Paroxetine Sertraline Sibutramine Terbutaline Trimethoprim Trimipramine

* Adverse reaction occurred more in women than in men.

The table, as amended, is an extract of the tables published on the website of the Center for Research on Therapeutics, University of Arizona ([http // www.torsades.org / medical_pros / drug-lists.htm #](http://www.torsades.org/medical_pros/drug-lists.htm)) to which we refer for more details

www.torsades.org); this list is regularly updated on the basis of recent indications. Table 1 illustrates a limited example of drugs classified in three distinct categories:

- 1) drugs correlated with a risk of TdP;
- 2) those potentially correlated with a risk of TdP;
- 3) those to be avoided in patients affected by the Long QT Syndrome (LQTS).

The first group, which includes methadone, accounts for psychiatric drugs such as haloperidol, chlorpromazine, droperidol, pimozide and thioridazine; the second group comprises clozapine, lithium, paliperidone, quetiapine, risperidone, venlafaxine and ziprasidone; the third group contains amitriptyline, citalopram, clomipramine, desipramine, doxepine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, trimipramine.

2. Antipsychotic drugs and prolongation of the QT interval

Evidence of the possible arrhythmic effect of antipsychotic drugs first became available in the 1960s, when several reports demonstrated a risk of TdP and sudden cardiac death correlated with treatment centring on thioridazine and mesoridazine [14]. The onset of alterations to cardiac rhythm during pharmacological treatment was initially viewed as an adverse event only affecting subjects who already had a cardiovascular disorder, but a large number of studies then demonstrated that drug-induced alterations of exactly that type also occurred in subjects not affected by cardiological conditions [17].

A study carried out over a three-year period (1985–1988) in Finland on 24,158 corpses analyzed by means of autopsy and toxicological tests, revealed that in approximately 49 subjects the cause of death could be “sudden death subsequent to administration of psychotropic drugs”, while adding that 46 of these individuals had been taking therapeutic doses of a phenothiazine, namely thioridazine [16].

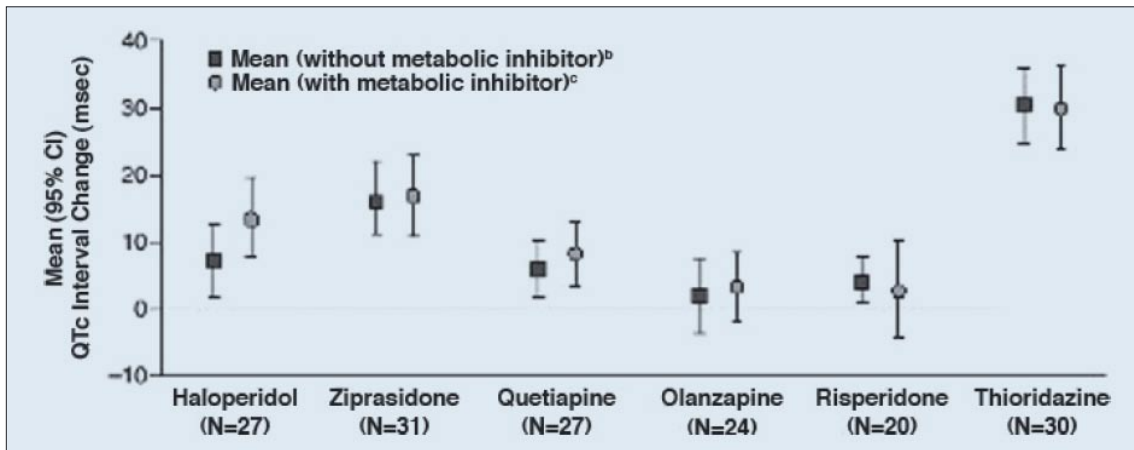


Figure 1. Changes in QTc from baseline with and without metabolic inhibitors
 b = risperidone, 6-8 mg/die
 c = risperidone, 16 mg/die

In the literature numerous studies have provided evidence of an association of other antipsychotic compounds carrying a risk of inducing prolonged QTc [2, 6, 8]; on the other hand, unlike the findings reported for thioridazine, none of these drugs turn out to have been implicated in the onset of TdP. Likewise, although many case reports have been published in the literature on the onset of TdP after treatment with haloperidol, most of these cases involved subjects taking extremely high intravenous doses of the drug (up to 825 mg/24h) [11].

An open label study [10] performed to assess the effect of six different antipsychotics (thioridazine, haloperidol, olanzapine, risperidone, quetiapine and ziprasidone) on the QT interval revealed that thioridazine (30.1 msec) and ziprasidone (15.9 msec) showed the highest increase, while the lowest was recorded in subjects undergoing treatment with olanzapine (1.7 msec). Similar alterations were observed in patients undergoing concomitant treatment with P450 cytochrome inhibitors for each of the groups tested (Figure 1).

Behind thioridazine and ziprasidone, a group undergoing treatment with haloperidol displayed the highest degree of prolongation of the QTc interval (7.1 msec). The latter finding, in line with other studies [23], appears to reflect the IC₅₀ of the various compounds, an important biochemical parameter indicating the minimum concentration of the specific substance required to determine a 50% inhibition of a channel, an ionic current or any other type of biological parameter. A comparison between different drugs (Table 2) makes it clear that haloperidol features a markedly lower IC₅₀ than other antipsychotics; this gives the most plausible explanation for the increased propensity of the drug to inhibit hERG potassium channels and a correspondingly more marked lengthening of the QTc interval.

3. Antipsychotic drugs and cardiac risk

A recently published retrospective cohort study [19] carried out by a group of pharmacologists in Nashville, USA, to investigate a patient population aged between 30 and 74, has been given major coverage by the mass media in spreading the information that the use of second generation antipsychotic drugs, known as ‘atypical antipsychotics’, doubles the risk run by patients of sudden cardiac death. A risk of sudden death has long been reported too for first generation antipsychotics, known as ‘typical antipsychotics’.

However, in the study under discussion the figures for the incidence of sudden cardiac death in patients undergoing treatment with typical and atypical antipsychotics were remarkably similar: approximately 1 out of 340 person-years in patients undergoing treatment with typical antipsychotics and 1 out of 360 person-years in those treated with atypical antipsychotics, compared to an incidence of 1 out of 700 person-years in individuals with similar characteristics not undergoing treatment with antipsychotics. The risk increased in a dose- and age-dependent manner.

Drugs	IC ₅₀
Haloperidol	1nM
Risperidone	167 nM
Quetiapine	5765 nM
Olanzapine	6013 nM

Therefore, the study under review here argues that second generation antipsychotic drugs are no safer than their first generation counterparts, at least with respect to severe adverse cardiac events. The authors hypothesize that a higher incidence of sudden cardiac death is secondary to the onset of fatal arrhythmias, and is probably caused by the inhibitory action of the drugs on potassium channels, resulting in a prolongation of the cardiac repolarization rate.

Compared to antipsychotics of the first generation, those of the second generation are less likely to elicit extrapyramidal symptoms, tardive dyskinesias, and malignant neuroleptic syndromes, although they are more likely to induce weight gain and other metabolic disorders. Aripiprazole [9] features a lower likelihood of inducing a lengthening of the QT interval, one of the possible mechanisms underlying the modest increase in overall risk of sudden death in patients treated with antipsychotic drugs.

It should, however, be emphasized that in a patient with symptoms clearly indicating a need for treatment with antipsychotic drugs, the potential consequences produced by failure to administer these drugs may well exceed the risks involved in their use.

4. Regulations governing the use of psychoactive drugs carrying the potential risk of prolonging the QTc interval

On January 3rd 2005 the Italian Medicines Agency (AIFA), in agreement with regulatory bodies worldwide, issued a directive providing for the withdrawal from the market of thioridazine by the deadline of June 30th 2005 after “cases of prolongation of the QT interval, cardiac arrhythmias and sudden death” that had been reported in schizophrenic subjects undergoing treatment with the drug.

Two years later, the Official Gazette of the Italian Republic, no. 60, dated March 30th 2007, published a directive issued by the Italian Medicines Agency (AIFA) dated 28th February 2007 on the subjects of amendments made by manufacturers to product information sheets for several antipsychotic drugs. In the case of haloperidol, pimozide and droperidol, the modifications introduced focused on a series of contraindications to the use of the drugs under certain circumstances, including the presence of clinically significant cardiovascular disorders (recent myocardial infarction, heart failure, cardiac arrhythmias) and baseline conditions bringing a risk of cardiovascular events (lengthening of the QTc interval, family history of arrhythmia or TdP, low potassium levels). Furthermore, the concomitant use of other drugs capable of prolonging the QTc interval is prohibited, while recommendations were made to avoid prescribing concurrent treatment with other neuroleptics.

On product information sheets for drugs including amisulpiride, chlorpromazine, clotiapine, clozapine,

droperidol, levomepromazine, levosulpiride, perfenazine, promazine, quetiapine and risperidone, the warnings and precautions for use, interactions and adverse events were changed to include mention of the cardiovascular safety profile and problem of prolonging the QTc interval. Special emphasis was placed on the use of extreme caution in prescribing these drugs to patients affected by a past or present history of cardiovascular disorders or with a family history of prolongation of the QTc interval, advising against their concomitant use with other neuroleptics or electrolyte-altering drugs, and recommending a careful evaluation of the potential interactions of these drugs with other metabolic inhibitors. This directive enforced the document published by the Pharmacovigilance Working Party (technical committee of the European Medicines Agency, EMEA) entitled “Public Assessment Report on Neuroleptics and Cardiac Safety, in particular QT prolongation, cardiac arrhythmias, ventricular tachycardia and torsades de pointes” in May 2006, classifying the many antipsychotic drugs currently employed into three distinct categories on the basis of evidence reported in the literature with regard to the risk of prolonging QTc and inducing TdP (Table 3).

The list of antipsychotic drugs proposed by the Pharmacovigilance Working Party Group includes the drug olanzapine, not indicated afterwards in the AIFA directives for 2007 merely because the drug was already registered with EMEA; the criterion applied was that, even when modifications to product information details filed with EMEA were required, no further evaluations by regulatory bodies of other member states were needed, unlike the situation with other psychotic compounds that are only registered with national agencies.

The precautions for use and warnings provided for olanzapine, with specific regard to prolonging the QTc interval, should therefore be considered substantially similar to those reported for the group of antipsychotic drugs including quetiapine and risperidone. In a way contrary to the indications provided for the group comprising haloperidol, for the former group no contraindication is named with reference to the concurrent use of drugs capable of prolonging QTcs, but the warnings reported do advise against the concomitant use of other neuroleptics and/or other compounds displaying a similar risk of prolonging QTc intervals. In this connection, the directives’ marked impact on clinical practice, especially in a psychiatric context, has been clearly evident, focusing not only on the association between antipsychotics, but also on multiple drug treatment, including compounds belonging to other drug classes. It should be mentioned that on 14th February 2008 an AIFA Directive issued on 28th January 2008 was published in the Official Gazette of the Italian Republic, no. 38, referring to a risk of QT prolongation associated with lithium, one of the drugs most widely used in combination with antipsychotic drugs in patients undergoing a multiple drug treatment.

Table 3. Cardiac risk of some antipsychotics

Low	Medium	High
Loxapine Oxyperlina Perphenazine Pipotiazina Prochlorperazine Promazine Remoxipride	Amisulpride Benperidolo Chlorpromazine Clozapine Fluphenazine Flupentixolo Levomepromazine Olanzapine Quetiapine Risperidone Sulpiride Trifluoperazine Zotepina Zuclopenthixol	Haloperidol Pimozide Sertindole Ziprasidone

5. Lithium

Lithium has unique features; it stands out as the sole example of a single ion capable of eliciting a potent mood-stabilizing action by means of a pharmacological mechanism that still needs to be fully understood. The therapeutic effect of the drug is correlated with the serum concentration of the ion, the optimal value to be achieved in the treatment of bipolar disorders being approximately 0.8 mEq/L. As a general rule, lithium levels are assayed 12 hours after the last oral dose, and most of the adverse effects are triggered when serum levels exceed 1.5-2 mEq/L.

A majority of Authors concur that the adverse effects produced by lithium on the cardiovascular system are relatively rare and of secondary importance [18]. Unlike the vast majority of psychoactive drugs, lithium is generally devoid of significant effects on the QTc interval; it may, however, elicit an inhibitory effect on impulse generation and transmission to the atrium. Accordingly, the latter may determine a risk of rhythm and conduction disorders, thus possibly explaining the small number of reports mentioning the onset of arrhythmias, together with several cases of bradyarrhythmia. ECG may exhibit a flattening or inversion of the T wave, and cases of atrioventricular block have been reported. Moreover, hypercalcaemia displayed in the aftermath of lithium's effect on parathyroid glands may predispose subjects to conduction defects, in particular bradycardia.

Lithium has, however, been included in the list compiled by the Center for Research on Therapeutics, University of Arizona, as one of the drugs potentially associated with the onset of TdP. For this reason, besides ensuring compliance with the AIFA Directive dated 28th January 2008, an ECG should be performed prior to initiating treatment with the drug .

6. Carbamazepine and other mood stabilizers

Carbamazepine is a versatile drug featuring a wide array of therapeutic indications: an antiepileptic and mood stabilizer, it is also prescribed for the treatment of trigeminal neuralgia. The drug interferes with sodium channels and, in addition to acting as a potent enzyme inducer in the liver; it exerts a chinidine-like effect on cardiac conduction. Structurally similar to tricyclic antidepressants, the drug may delay intracardiac conduction and the suppression of ventricular activity.

A study carried out by Kenneback in 1991 [15] demonstrated that carbamazepine produced no significant effect at ECG on the QRS or the QT interval in patients with a normal heart rate. However, patients with a pre-existing heart disease or arrhythmias displayed symptomatic conduction defects. ECG monitoring should therefore be scheduled, even though carbamazepine is not included on the list of drugs that set up a predisposition to prolonging the QT interval.

Various other substances displaying putative mood stabilizing properties are currently available. These include valproate and topiramate, neither of which has come under suspicion of inducing adverse cardiac effects. During use of lamotrigine isolated cases of atrioventricular block or supraventricular extrasystoles have been reported. Rare reports of bradycardia or atrial fibrillation have been signalled in the course of treatment with gabapentin. In any case, none of the substances just mentioned have been included on the list of drugs that favour a prolongation of the QT interval.

7. Tricyclic antidepressants (TCA)

Tricyclic antidepressants (imipramine, desipramine,

amitriptyline, nortriptyline, clomipramine, trimipramine, doxepine, protriptyline, amoxapine) have played a key role in the history of the treatment of depressive disorders. They were the first class of antidepressant compounds to be widely employed in the treatment of depression, constituting the treatment of choice for approximately 25 years.

The adverse effects produced by these compounds implied the need for psychiatrists to become familiar with a broad variety of symptomatological pictures, including the Central Anticholinergic Syndrome (CAS) comprising delirium and hallucinations; other side-effects include orthostatic hypotension, worsening of acute glaucoma and cardiac conduction delay.

Of the four pharmacodynamic mechanisms underlying the major adverse effects induced by TCAs – anticholinergic effect, adrenergic action, 5-HT₂ activation and antihistamine activity – only the first two, together with chinidine-like activity, are capable of affecting the cardiovascular system [5].

Cardiac arrhythmia is the main cause of death from overdose. For many years this primary consideration, together with the possible incidence of other conditions (orthostatic hypotension, one of the most common reasons for suspending treatment with tricyclic antidepressants; tachycardia, associated with all tricyclic drugs, not only those with a preponderant anticholinergic activity leading – especially in elderly patients and if continuing for long periods – to an increase in cardiac burden, of potentially high clinical significance in patients with ischaemic heart disease), made physicians exceedingly wary of prescribing TCA to patients either with or without cardiac disorders. The effects produced by these substances have been described in detail: by inhibiting the Na⁺/K⁺ATPase pump, tricyclic antidepressants apparently stabilize the excitable membranes, producing a dose-dependent conduction delay, particularly of ventricular conduction through the His-Purkinje bundle. Thus, tricyclic antidepressants possess type Ia antiarrhythmic properties or chinidine-like effects [7].

In patients featuring a pre-existent cardiac conduction delay, therapeutic plasma concentrations of tricyclic antidepressants may produce positive effects on ventricular excitation; however, TCAs are also capable of eliciting a further delay in the conduction rate, leading to cardiac arrest. Prior to treatment, a QTc interval > 450 msec is indicative of the presence of an overt conduction delay; in these cases TCA should not be administered on account of the danger of worsening patients' conditions. High plasma concentrations of the drug imply an increased risk of cardiotoxicity; for example, concentrations of imipramine exceeding 350 ng/ml are known to increase a high-grade atrioventricular block.

Children below the age of 12 years display a greater susceptibility to the risk of sudden death during treatment with tricyclic antidepressants; cases of sudden

death have been reported in a limited number of children aged below 12 affected by attention/hyperactivity deficit (ADHD) who had been taking desipramine. It has been hypothesized that an immature conduction system may render some children more vulnerable to the cardiac effects of desipramine.

In view of the above problems of cardiac tolerability, associated with the recent finding of a good safety profile for sertraline (SSRI) [22] in treating depressed patients after myocardial infarction, the use of TCA is largely contraindicated in patients affected by ischaemic heart disease, and these drugs should be administered only to patients who fail to respond positively to other drugs.

8. Other antidepressants

The antidepressant venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has shown greater efficacy in inhibiting the reuptake of serotonin (5-HT) than noradrenaline (NA); *in vitro* studies have indicated a higher, almost 8-fold affinity of venlafaxine for the 5-HT than for the NA transporter. It appears, therefore, that at low doses (75–150 mg/die) venlafaxine acts prevalently on serotonin, later inhibiting reuptake by both neurotransmitters in a dose-dependent fashion.

A wide variety of symptoms comprising ECG abnormalities (lengthening of the QT interval, branch block, prolongation of QRS), sinus and ventricular tachycardia, bradycardia, hypertension, alteration of consciousness (from lethargy to coma), serotoninergic syndrome and comitial crisis have been reported in cases of acute but non-fatal venlafaxine overdose.

At doses exceeding 200 mg/die, venlafaxine is capable of inducing prolongation of the QT interval in young healthy adults [12]. Data reported by coroners in England and Wales between 1998 and 2000 have implicated venlafaxine in 12.7 deaths per million prescriptions, which was substantially higher than for SSRIs and at a level similar to that for tricyclic antidepressants (1.9 and 12.6 deaths per million prescriptions, respectively) [4].

Duloxetine is another serotonin-noradrenaline reuptake inhibitor (SNRI). Compared to venlafaxine, duloxetine appears to achieve a better balance between the two pathways, producing a more marked influence on NA than 5-HT reuptake.

Clinical trials have demonstrated the good degree of safety and tolerability of duloxetine when administered at a dose ranging between 40 and 120 mg/die. A slight but significant increase in heart rate (tachycardia) has been reported even at low doses of the drug [21].

Duloxetine does not appear to produce any significant adverse effects on cardiac repolarization or the QT interval. A clinical trial performed [25] using duloxetine doses higher than those prescribed for therapeutic purposes (400 mg/die) demonstrated a decrease in QTc, not exceeding 36 msec with respect to baseline values, with no subjects displaying a QTc > 445 msec.

Citalopram may determine a non-specific, clinically insignificant prolongation of the QT interval; escitalopram appears to elicit effects similar to those obtained with citalopram. After citalopram overdoses, a prolongation of the QT interval has been observed [13].

9. Conclusions

To conclude, psychiatric patients undergoing pharmacological treatment – with particular reference to subjects affected by psychotic disorders – are notably susceptible to severe cardiac disorders, including rhythm abnormalities, ischaemic heart disease and myocarditis, but also to a wide array of associated risk factors. To be specific, these comprise type II diabetes mellitus, metabolic disorders, obesity, cigarette smoking and substance use, as well as other hazardous practices. Further studies should now be undertaken to assess the problem of prolongation of the QT interval in various clinical contexts.

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