REVIEW ARTICLE

Cardiac Effects of Psychotropic Drugs

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Abstract

***Introduction**: The incidence of mortality is higher among psychiatric patients than among the general population and the cause of which may be the psychiatric disorder itself or other related factors like life-style and medications. Sudden death has been associated with certain psychotropic drugs and the underlying cause(s) have been suggested to be some adverse cardiac complications. We reviewed the literature for the cardiac effects attributed to psychotropic drugs. **Methods**: A Medline and manual search of the literature on the cardiac effects attributed to the psychotropic drugs was performed. We limited ourselves to the main psychotropic drugs (antipsychotics, antidepressants, mood stabilisers, and benzodiazepines) that are available in Singapore. **Results**: The search showed that certain drugs carry a greater potential for adverse cardiac complications. Among the antipsychotics, thioridazine has a greater risk for cardiac events. The tricyclic antidepressants also have significant effect on the heart rate, blood pressure as well as having the propensity to cause prolonged QTc, whereas the selective serotonin reuptake inhibitors (SSRIs) are generally safe. Among the mood stabilisers, lithium and carbamazepine have been associated with sinus node arrhythmias while sodium valproate is relatively free of any untoward cardiac effect. The benzodiazepines are in general safe even in patients with myocardial infarction and coronary bypass. **Conclusions**: In patients with higher risk of cardiac complications (elderly, pre-existing cardiac disorders, concurrent medications with potential cardiac effects and poor metabolisers), the choice of psychotropic drugs where indicated has to be considered with these factors in mind as well as the inherent risk of these psychotropic drugs. Monitoring of the blood pressure, heart rate and ECG should be done regularly.*

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Key words: Antidepressants, Arrhythmias, Hypotension, Mood stabilisers, Myocardial infarction, Psychotropic drugs, QTc interval

Introduction

The incidence of mortality is higher among psychiatric patients than among the general population and the cause of which may be the psychiatric disorder itself or other related factors like life-style and medications.[1,2] Reports of sudden deaths among patients taking psychotropic drugs have raised concerns that some of the deaths might have been from cardiac arrhythmias induced by these drugs.[3] Many of the commonly prescribed psychotropic drugs have potential cardiac effects, either directly from their effect on the myocardium or on the conduction system of the heart; or indirectly from hypotension or tachycardia. The use of these drugs is by no means uncommon. In a survey of 534 inpatients with chronic schizophrenia in Woodbridge Hospital, we found that 59% of the patients were receiving two or more antipsychotic medications, 24% were receiving a benzodiazepine, 14% were on a mood stabiliser (lithium, sodium valproate or carbamazepine), 7% were prescribed a tricyclic antidepressant and 4% were receiving a selective serotonin reuptake inhibitor (SSRI).[4]

In this article, we review the literature on the effects of these psychotropic drugs on the heart. We performed a manual and Medline search of the available literature in the English language from the year 1966 to October 2000 and limited ourselves to the main psychotropic drugs that are available in Singapore.

The drugs reviewed include the first-generation antipsychotics (haloperidol, trifluperazine, pimozide, chlorpromazine, thioridazine, fluperazine, pipothiazine and zuclopenthixol); second-generation antipsychotics (clozapine, risperidone, olanzapine, amisulpride and quetiapine); tricyclics antidepressants (TCAs) (imipramine, amitriptyline, clomipramine and dothiepin); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram); reversible inhibitor of monoamine oxidase (moclobemide); atypical anti-depressants (mirtazapine, nefazodone, venlafaxine and tianeptine); mood stabilisers (lithium, sodium valproate and carbamazepine) and benzodiazepines (alprazolam, bromazepam, diazepam, loramet and lormetzepam).

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Heart Rate and Postural Hypotension

The side effects of tachycardia and hypotension result from the blockade of muscarinic receptors and alpha-1 adrenoreceptors by psychotropic drugs. The type-2 muscarinic receptors (M2) are responsible for vagal inhibition through increased potassium conductance and inhibition of calcium channels, blockade of these receptors leads to tachycardia. The vagal preganglionic neurons, which project to the heart, are also tonically inhibited by endogenous gamma-aminobutyric acid (GABA).

Constriction of veins is mediated mainly by alpha-1 adrenoceptors and blockade of these receptors leads to vasodilation. This primarily results in postural hypotension from the pooling of blood in the major veins upon assuming an upright posture. This vasodilation in turn leads to reflex tachycardia and may worsen angina due to the increased myocardial oxygen demand.

Antipsychotic Drugs

All antipsychotic drugs have antimuscarinic effects to a greater or lesser extent. These effects often remit with time and rarely cause clinically significant symptoms. Postural hypotension was reported in 77% of people receiving antipsychotic drugs versus 15% receiving placebos.[5] Among the second-generation antipsychotic medications, olanzapine has relatively less potent antimuscarinic properties and is reported to produce no changes in heart rate when compared with placebo.[6] Clozapine, on the other hand, has potent antimuscarinic effects and tachycardia occurs in 20% to 30% of patients treated with clozapine.[7] There is a single case report of a patient developing postural hypotension and cardiac arrest during risperidone therapy.[8]

Quetiapine, through its blockade of the alpha-1 adrenergic receptors, causes some postural hypotension. More than 20% of elderly patients receiving quetiapine (100 to 200 mg/day) showed increase in heart rate of 20 beats/min or more or a decrease in systolic blood pressure of 30 mmHg or greater.[9]

Other than its high affinity for dopamine D2 and D3 receptor subtypes, amisulpride has no appreciable affinity for other receptors. Coulouvrat and Dondey-Nouvel[10] reviewed 11 clinical studies and reported a slight decrease in heart rate (defined as any sitting or supine heart rate ≤50 beats/min and decrease versus baseline ≤15 beats/minute) in 1% of patients. These patients remained clinically asymptomatic and there were no ECG abnormalities.

Antidepressants

Tricyclic antidepressants (TCAs) at therapeutic dosages have significant effects on the heart related to their antimuscarinic properties, which are mainly seen as an increased heart rate.[11] The alpha-1 adrenergic antagonism by TCAs also results in postural hypotension.[12] Of the SSRIs, fluvoxamine has been reported to cause decreases in recumbent systolic blood pressure in patients.[13] Tachycardia was one of the most common features in fluoxetine overdose.[14] Anecdotal reports exist of supraventricular tachycardia occurring with fluoxetine at therapeutic dose range[15] and of sinus bradycardia in a patient taking fluoxetine and pimozide.[16]

Mirtazapine is an antagonist of presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors on both norepinephrine and serotonin presynaptic axons. Analysis of the data from the clinical trial development programme in the US and Europe showed that no changes in heart rate and blood pressure occurred with mirtazapine treatment.[17] Bremner et al[18] reporting on 6 cases of mirtazapine overdose reported that there were no serious adverse effects of overdose. However, Tulen et al[19] reported that after 4 weeks of treatment, patients with unipolar affective disorder showed increased heart rate and decreased heart rate variability. This was attributed to mirtazapine's weak anticholinergic properties resulting in vagal inhibition. However, it had no effect on blood pressure or blood pressure variability.

Venlafaxine has no appreciable muscarinic or adrenergic receptor activity although sinus tachycardia has been reported.[20] A potential adverse effect is the development of hypertension from the inhibition of noradrenaline re-uptake. Increases in diastolic blood pressure of 15 mmHg or more have been reported in up to 6% of patients on venlafaxine, although other studies did not report this finding and is unlikely to be of clinical significance.[21] Nefazodone has no significant alpha-1 adrenergic or muscarinic activity; however, the drug insert reported postural hypotension in 3% of patients on clinical trials. Trazodone has been shown to have no appreciable effect on the heart rate.[22]

Mood Stabilisers

White and Santos[23] reported a case of severe hypotension in an 11-year-old child with status epilepticus after being treated with intravenous valproate. We found no published report linking carbamazepine with hypotension.

Benzodiazepines

It has been suggested that benzodiazepines reduce the vagal tone and thereby increase the heart rate.[24] However, this effect does not seem to be clinically significant as benzodiazepines have been shown to be effective and safe in treating the anxiety associated with myocardial infarction and coronary bypass.[25,26]

Cardiac Arrhythmias

One of the mechanisms by which some psychotropic

drugs may cause sudden death is by inducing cardiac arrhythmias by their effects on the conduction system of the heart. These actions are similar to those of the anti-arrhythmic drug, quinidine, and involve sodium, potassium and calcium channel's blockade. On the ECG, these effects may appear as broadening of the QRS complex (prolongation of the QT interval, abnormalities of the T waves, and/or prominent U waves). As the QT interval varies with the heart rate, this is adjusted for in the corrected QT interval (QTc). QTc prolongation is associated with the development of polymorphic ventricular tachycardia including torsade de pointes, and it has been reported to be an independent risk factor for sudden death presumably from ventricular arrhythmias.[27]

Antipsychotic Drugs

Long-term treatment with antipsychotic drugs in conventional doses prolonged both QTc and QTc dispersion.[28] Most of the conventional (first generation) antipsychotic medications including thioridazine, pimozide, haloperidol and chlorpromazine have been reported to cause QTc lengthening.[29,30] However, the risk seems to be substantially higher with thioridazine[31] with a rate of cardiac complications (QRS and QT prolongation) equal to or higher than that of TCAs.[32]

Pimozide is another antipsychotic that has been implicated in QT prolongation and torsades de pointes. Forty reports (16 deaths) of serious cardiac reactions with pimozide use have been reported between 1971 and 1995.[33] An increase of QT (mean change of only 1.3 ms) has been reported in 5% of patients treated with olanzapine, which is not statistically different from placebo.[6] Increase of mean QTc of up to 8 ms has been reported with quetiapine use.[34] There is a case report of a patient developing postural hypotension, prolonged QTc interval and subsequently cardiac arrest during risperidone therapy.[8] However, data from 10 studies indicate that mean QTc changes in patients receiving risperidone were negative or minimally positive.[35] It has also been reported that clozapine can cause ventricular tachycardia and atrial fibrillation.[36]

There is a case report of a patient with amisulpride overdose who developed seizures, hyperthermia, minimal extrapyramidal side effects, tachycardia and slight prolongation of QT interval.[37] The risk factors for prolonged QTc are increasing age and higher doses.[31] Other factors, such as electrolyte imbalances, coincident cardiac disease, stress and extremes of emotion or physical exertion including restraint procedures, may predispose the patient to arrhythmia.[38]

Antidepressants

Overdoses of TCAs like amitriptyline, doxepin, imipramine and clomipramine have been associated with QTc prolongation and ventricular arrhythmias.[39,40] Sudden deaths have been reported with clomipramine and imipramine.[41] However, a recent study by Reilly et al[31] suggested that even at therapeutic doses, TCAs prolong the QT interval independent of any cardiac problems. The TCAs have also been associated with the Brugada's sign i.e., right bundle branch block and elevation of the ST segment,[42] which has been linked to sudden death from ventricular fibrillation.

The SSRIs have a generally benign cardiovascular profile.[43] However, there are anecdotal reports of QTc prolongation with fluoxetine poisoning[44] and at therapeutic dose in a healthy 74-year-old woman taking no other medications.[45]

There are case reports of tachycardia, right axis deviation, prolonged QT interval and T wave changes with venlafaxine overdose.[46,47] Trazodone like the tricyclic antidepressants prolongs ventricular polarisation seen as an increase in the QTc interval and decreased T wave height.[48] Van de Merwe et al, [49] however, reported that the increased QTc, reduced heart rate and increased PR interval emerged only in the initial part of treatment but disappeared subsequently.

Mood Stabilisers

Lithium has been known to cause symptomatic sinus node bradyarrhythmias. This effect of lithium on the sinus node seems to be intrinsic and not the result of increased parasympathetic tone. Lithium replaces intracellular potassium[50] and may lead to electrophysiological changes including reduced electrical impulse propagation. Rosenqvist et al[51] reported the presence of moderate sinus node dysfunction (sinus arrest >1.5 s, minimum heart rate <56 beats/min) in 56% of patients in a lithium-treated group (without any known cardiovascular disease, or concomitant chronotropic medication) compared with 30% in an age-stratified reference population of healthy individuals. The authors also found that among individuals with pacemakers, 0.46% had treatment with lithium and concluded that clinically significant dysfunction is uncommon.

It is well documented that lithium has some inhibitory effect on impulse generation and transmission within the atrium and that it poses other risks for rhythm disturbances and conduction defects[52] with advancing age as a risk factor.[53] T wave depression may occur in up to 20% of patients treated with lithium.[54] Reversible atrioventricular block (first degree), sinoatrial dysfunction, bradycardia and sinus pauses have been observed even within the therapeutic serum level range, mostly in elderly patients.[55]

Carbamazepine is also known to cause sinus node, AV node and Purkinje conduction disturbances. Kasarskis et

al[56] reviewed the literature and defined two distinct clinical cardiac syndromes. The first group consisted of predominantly younger patients with massive self-induced carbamazepine overdoses who developed persistent sinus tachycardia although not life threatening. The second group consisted of older female patients with carbamazepine-induced bradycardia or A-V conduction delays, which can occur with therapeutic or modestly elevated levels. A report by Ladefoged and Mogelvang[57] speculated that carbamazepine may unmask a latent AV conduction defect in older patients, causing varying degrees of heart block even at therapeutic levels.

Benzodiazepines

Mullins[58] reported a case of alprazolam overdose in a man who developed marked first-degree atrioventricular block and suggested that it could have resulted from blockade of the calcium channel.

Myocardial Ischaemia/Infarction

Antidepressants

Thorogood et al[59] found an incidental 17-fold increase in the risk of myocardial infarction [relative risk (RR), 16.9; 95% confidence interval (CI), 3.9-72.8] in women aged 16 to 39 years receiving psychotropic drugs. Lapane et al[60] reported an association between antidepressants (excluding fluoxetine) and ischaemic heart disease (IHD) (RR, 2.0; 90% CI, 1.1-3.9). Likewise, Cohen et al[61] reported an association between use of tricyclic antidepressants (but not SSRIs) with an increased risk of myocardial infarction. They reported a more than two-fold increased risk of myocardial infarction in health plan members who received prescription of tricyclic agents compared with those with no antidepressant use. They concluded that tricyclic antidepressants aggravate the cardiovascular effects of depression and that SSRIs do not carry this increased risk. A possibility of the purported link between TCAs and myocardial infarction is that TCAs could somehow contribute to this adverse cardiac event.[62] On the other hand, it could have been the psychiatric conditions for which these drugs were prescribed that are associated with myocardial infarction. For instance, panic attacks have been associated with IHD[63,64] and hyperventilation, which is one of the cardinal features of panic disorder, can cause coronary artery spasm which in turn can lead to myocardial infarction. Chronic stress, which increases cardiac sympathetic input, could contribute to the initiation and progression of atherosclerosis.[65] The apparent association of ischaemia/infarct in patients treated with TCAs and not SSRIs could be that TCAs do not counteract the elevated risk resulting from depression whereas SSRIs do so.[66] Among the atypical antidepressants, we found only one reported case of an elderly woman with a history of IHD and who developed an acute ischaemic attack within the first week of venlafaxine treatment.[67]

Antipsychotics

Ketch et al[68] described a man without coronary heart disease who developed ST elevation subsequent to clozapine therapy for which none of the usual causes were found. The ST segment returned to baseline after clozapine was stopped.

Mood Stabilisers

Perrier et al[69] reported a case of severe lithium intoxication in a patient who presented with myocardial infarction and as the myocardial injury was segmental, the authors proposed a probable vascular aetiology, such as prolonged coronary artery spasm, rather than a toxic effect of lithium on myocardial cells.

Benzodiazepines

Benzodiazepines appear safe and are often used as anxiolytics in cardiac patients (in the aftermath of a myocardial infarction and well as those recovering from a coronary pass).[26,70]

Other Adverse Cardiac Effects

Cardiomyopathy and myocarditis have been reported in patients treated with antipsychotic medications, although a causal link with clozapine seems more likely with an incidence of at least 0.29% in one series.[71] Autopsy results of 6 fatal cases of myocarditis and cardiomyopathy revealed eosinophils and myocytolysis consistent with an acute drug reaction.[72]

Genetic Factors and Psychotropic Drugs

One of the main isoenzymes involved in the metabolism of a large number of these psychotropic drugs is CYP2D6. Genetic polymorphisms exist for these enzymes and, in some instances, confer different metaboliser status; those with normal rates of metabolism being classified as "extensive metabolisers" and those with reduced metabolism being referred to as "poor metabolisers". In the case of CYP2D6, the proportion of "poor metabolisers" for Caucasians ranges between 5% and 10%, but is less than 1% in Asians.[73] These "poor metabolisers" will not only be missing the hepatic component of CYP2D6 mediated metabolism, but will also lack the right ventricular CYP2D6 expression.[74,75] Thus, both presystemic and target tissue metabolism of most TCAs and antipsychotic drugs in these individuals may render them to be more vulnerable to the cardiotoxic effects of some of these drugs. Chinese "extensive metabolisers" also tend to have slightly slower metabolic rates compared with Caucasian "extensive metabolisers" due to the presence of a special allele.[76] Therefore, these individuals may also be more susceptible

to the adverse effects of psychotropic drugs.

Comments and Conclusions

Taking these published reports into consideration, certain drugs carry a greater potential for adverse cardiac complications. Tempering this, however, is the fact that the majority of these cardiac effects comprised anecdotal reports and the validity of reports of this nature is often questioned.[77] Venning[77] suggested that the criteria of validity should include the following: whether the adverse effect is consequent on the expected pharmacological action of the drug, or was the event an immediate adverse reaction, or it recurred with rechallenge or it was a repetition of a rare event. Clinicians should incorporate these criteria in assessing the validity of such reports. Table I summarises the side effects of commonly used psychotropic drugs.

The risk of adverse effects is also increased in individuals with pre-existing cardiac illness or electrolyte imbalances. Genetic characteristics also increase the risk of cardiac adverse effects. Other risk factors include increasing age and the need for usage of higher doses of psychotropic drugs.

Drug-drug interaction is also an important consideration. Drugs like antiarrhythmic agents (quinidine, procainamide), antihistaminics (terfenadine) and antimicrobials (erythromycin, chloroquine) have a propensity to prolong the QT interval. The concurrent prescription of these agents with an antipsychotic medication could have a synergistic additive effect. Inhibition of the cytochrome P450 enzymes involved in the metabolism of antipsychotic and antidepressant drugs which leads to increased blood levels of these drugs and prolongation of the QT interval in individuals taking antipsychotic medications, such as haloperidol, sertinole, risperidone and olanzapine, have been reported to occur in a concentration-related manner.[78] Certain SSRIs (fluoxetine, fluvoxamine, paroxetine) are potent inhibitors of some of these cytochrome P450 enzymes and the concomitant use of these drug with another psychotropic drug may increase the risk of an adverse cardiac event.

An ideal psychotropic drug would be one that is devoid of psychiatric, extrapyramidal and peripheral adverse effects at therapeutic dosage. However, no existing antipsychotic drug fulfills the criteria. The pharmacological and clinical data on the existing drugs and their risk for cardiovascular toxicity is not sufficient to rank these drugs in terms of their side effects. Therefore, for patients in whom cardiac complications are likely, e.g. the elderly, those with pre-existing cardiac disorders, those on concurrent medications with potential cardiac effects and poor metabolisers, the choice of psychotropic drugs where indicated has to be considered with these factors in mind as well as the inherent risk of these psychotropic drugs. The clinician must consider the risk-benefit ratio and monitoring of blood pressure, heart rate and ECG should be done regularly in this group of patients.

Lastly, large-scale epidemiological studies must be done to establish the link between psychotropic drugs and their peripheral side effects.

TABLE I: IMPORTANT CARDIAC EFFECTS OF PSYCHOTROPIC DRUGS

	Cardiac effects
Antipsychotic drugs	
• Thioridazine, pimozide, chlorpromazine, risperidone, haloperidol	QTc prolongation
• Clozapine	Tachycardia
Antidepressant	
• Tricyclic antidepressants	QTc prolongation, postural hypotension, tachycardia
Mood stabilisers	
• Carbamazepine	Sinus node arrhythmias
• Lithium	Bradyarrhythmias, A-V block

REFERENCES

1. Harris E C, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998; 173:11-53.
2. Ruschena D, Mullen P E, Burgess P, Cordner S M, Barry-Walsh J, Drummer O H, et al. Sudden death in psychiatric patients. Br J Psychiatry 1998; 172:331-6.
3. Appley L, Thomas S, Ferrier N, Lewis J G, Shaw J, Amos T. Sudden unexplained death in psychiatric in-patients. Br J Psychiatry 2000; 176:405-6.
4. Chong S A, Sachdev P, Mahendran R, Chua H C. Neuroleptic and anticholinergic drug use in Chinese patients with schizophrenia resident in the state psychiatric hospital in Singapore. Aust N Z J Psychiatry 2000; 34:988-91.
5. Silver H, Kogan H, Zlotogorski D. Postural hypotension in chronically medicated schizophrenics. J Clin Psychiatry1990; 51:459-62.
6. Barnes T R E, McPhillips M A. Critical analysis and comparison of the side effects and safety profiles of the new antipsychotics. Br J Psychiatry 1999; 174(Suppl 38):4S-43S.
7. Grohmann R, Ruther E, Sassim N, Schmidt L G. Adverse effects of clozapine. Psychopharmacology 1989; 99:S101-4.
8. Ravin D S, Levenson J W. Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997; 31:867-70.
9. Garver D L. Review of quetiapine side effects. J Clin Psychiatry 2000; 61(Suppl 8):31-3.
10. Coulouvrat C, Dondey-Nouvel L. Safety of amisulpride: a review of 11 clinical studies. Int Clin Psychopharmacol 1999; 14:209-18.
11. Roos J C. Cardiac effects of the antidepressant drugs. A comparison of the tricyclic antidepressants and fluvoxamine. Br J Clin Pharmacol 1983; 15(Suppl 3):439S-45S.

12. Warrington S J, Padgham C, Lader M. The cardiovascular effects of antidepressants. Psychol Med Monogr Suppl 1989; 16:1-40.
13. Saletu B, Schjerve M, Crunberger J, Schanda H, Arnold O H. Fluvoxamine—a new serotonin re-uptake inhibitor: first clinical and psychometric experiences in depressed patients. J Neural Transm 1977; 41:17-36.
14. Borys D J, Setzer S C, Ling L J, Reisdorf J J, Day L C, Krennzelok E. Acute fluoxetine overdose: a report of 234 cases. Am J Emerg Med 1992; 10:115-20.
15. Gardner S F, Rutherford W F, Munger M A, Panacek E A. Drug induced supraventricular tachycardia: A case report of fluoxetine. Ann Emerg Med 1991; 20:194-7.
16. Ahmed I, Dagincourt P G, Miller L G, Shader R I. Possible interaction between fluoxetine and pimozide causing sinus bradycardia. Can J Psychiatry 1993; 38:62-3.
17. Montgomery S A. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995; 10(Suppl 4):37-45.
18. Bremner J D, Wingard P, Walshe T A. Safety of mirtazapine in overdose. J Clin Psychiatry 1998; 59:233-5.
19. Tulen J H, Bruijn J A, deMan K J, Pepplinkhuizen L, van den Meiracker A H, Man in't Veld A J. Cardiovascular variability in major depressive disorders and effects of imipramine on mirtazapine (Org 3770). J Clin Psychopharmacol 1996; 16:135-45.
20. Rudolph R L, Derivan A T. The safety and tolerability of venlafaxine hydrochloride: analysis of the clinical database. J Clin Psychopharmacol 1996; 16(2 Suppl 3):54S-9.
21. Feighner J P. Cardiovascular safety in depressed patients: focus on venlafaxine. J Clin Psychiatry 1995; 56:574-9.
22. Hayes R L, Gerner R H, Fairbanks L, Moran M, Waltuch L. ECG finding in geriatric depressives given trazodone, placebo, or imipramine. J Clin Psychiatry 1983; 44:180-3.
23. White J R, Santos C S. Intravenous valproate associated with significant hypotension in the treatment of status epilepticus. J Child Neurol 1999; 14:822-3.
24. Adinoff B, Mefford I, Waxman R, Linnoila M. Vagal tone decreases following intravenous diazepam. Psychiatry Res 1992; 41:89-97.
25. Hollister L E, Muller Orlinghausen B, Richels K, Shader R I. Clinical uses of benzodiazepines. J Clin Psychopharmacol 1993; 13:161S-9.
26. Roy-Bryne P P, Cowley D S, editors. Benzodiazepenes in clinical practice: risks and benefits. Washington, DC: American Psychiatric Press, 1991.
27. Algra A, Tijssen J, Roellandt J R, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991; 83:1888-94.
28. Kitayama H, Kiuchi K, Nejima J, Katoh T, Takano T, Hayakawa H. Long-term treatment with antipsychotic drugs in conventional doses prolonged QTc dispersion, but did not increase ventricular tachyarrhythmias in patients with schizophrenia in the absence of cardiac disease. Eur J Clin Pharmacol 1999; 55:259-62.
29. Thomas S H L. Drugs, QT interval abnormalities and ventricular arrhythmias. Adverse Drug React Toxicol Rev 1994; 13:77-102.
30. Barnes T R E, McPhillips M A. Critical analysis and comparison of the side effect and safety profiles of the new antipsychotics. Br J Psychiatry 1999; 174(Suppl 38):34-43.
31. Reilly J G, Ayis S A, Ferrier I N, Jones S J, Thomas S H. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 355:1048-52.
32. Buckley N A, Whyte I M, Dawson A H. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. Clin Toxicol 1995; 33:199-204.
33. Committee on Safety of Medicines-Medicines Control Agency. Cardiac arrhythmias with pimozide. Curr Probl Pharmacovigilance1995; 35: 290-1.
34. Arvanitis L A, Miller B G, The Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997; 42:233-46.
35. Conley R R. Risperidone side effects. J Clin Psychiatry 2000; 61(Suppl 8):20-3.
36. Varma S, Achan K. Dysrhythmia associated with clozapine. Aust N Z J Psychiatry 1999; 33:118-9.
37. Traqui A, Mutter-Schmidt C, Kintz P, Berton C, Mangin P. Amisulpride poisoning: a report on two cases. Hum Exp Toxicol 1995; 14:294-8.
38. Royal College of Psychiatrists. The Association between Antipsychotic Drugs and Sudden Death. Council Report CR57. London: Royal College of Psychiatrists, 1997.
39. Giradina E G V, Gigger J T, Glassman A H, Perel J M, Kantor S J. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979; 60:1045-52.
40. Yap Y G, Camm J. Risk of torsades de pointes with non-cardiac drugs. Doctors need to be aware that many drugs can cause QT prolongation. BMJ 2000; 320:158-9.
41. Swanson J R, Jones G R, Krasselt W, Denamark L N, Ratti F. Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy: a review of the literature and possible mechanism. J Forensic Sci 1997; 42:335-9.
42. Brugada P, Brugada J. Right bundle branch block, persistent ST elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicentre report. J Am Coll Cardiol 1992; 20:1391-6.
43. Stoudemire A. New antidepressant drugs and the treatment of depression. Psychiatr Clin North Am 1995; 19:495-514.
44. Graudins A, Vossler C, Wang R. Fluoxetine-induced cardiotoxicity with response to bicarbonate therapy. Am J Emerg Med 1997; 15: 501-3.
45. Appleby M, Mbewu A, Clarke B. Fluoxeine and ventricular torsase—Is there a link? Int J Cardiol 1995; 49:178-80.
46. Fantaskey A, Burkhart K K. A case report of venlafaxine toxicity. J Toxicol Clin Toxicol 1995; 33:359-61.
47. Blythe D, Hackett L P. Cardiovascular and neurological toxicity of venlafaxine. Hum Exp Toxicol 1999; 18:309-13.
48. Burgess C D, Hames T K, George C F. The electrocardiographic and anticholinergic effects of trazodone and imipramine in man. Eur J Clin Pharmacol 1982; 23:417-21.
49. Van de Merwe T J, Silverstone T, Ankier S I. Electrophysiological and haemodynamic change with trazodone, amitriptyline and placebo in depressed patients. Curr Med Res Opin 1984; 9:339-52.
50. Singer I, Rotenberg D. Mechanism of lithium action. N Engl J Med 1973; 289:254.
51. Rosenqvist M, Bergfeldt L, Aili H, Mathe A A. Sinus node dysfunction during long-term lithium treatment. Br Heart J 1993; 70:371-5.
52. Mitchell J E, Mackenzie T B. Cardiac effects of lithium therapy in man: a review. J Clin Psychiatry 1982; 43:47-51.
53. Roose S P, Bone S, Haidorfer C, Dunner D L, Fieve R R. Lithium treatment in older patients. Am J Psychiatry 1979; 136:843-4.
54. Schou M. Electrocardiographic changes during treatment with lithium and with drugs of the imipramine type. Acta Psychiatr Scand 1963; 169(Suppl):258-9.

55. Jaffe C. First-degree atrioventricular block during lithium carbonate treatment. Am J Psychiatry 1977; 136:701-8.
56. Kasarskis E J, Kuo C S, Berger R, Nelson K R. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. Arch Intern Med 1992; 152:186-91.
57. Ladefoged S D, Mogelvang J C. Total atrioventricular block with syncopes complicating carbamazepine therapy. Acta Med Scand 1982; 212:185-6.
58. Mullins M E. First degree atrioventricular block in alprazolam overdose reversed by fumazelin. J Pharm Pharmacology 1999; 51:367-70.
59. Thorogood M, Cowen P, Mann J, Murphy M, Vessey M. Fatal myocardial infarction and use of psychotropic drugs in young women. Lancet 1992; 340:1362.
60. Lapane K L, Zierler S, Lasater T M, Barbour M M, Carleton R, Hume A L. Is the use of psychotropic drugs associated with increased risk of ischaemic heart disease? Epidemiology 1995; 6:376-81.
61. Cohen H W, Gibson G, Alderman M H. Excess risk of myocardial infarction in patients treated with antidepressant medications: Association with use of tricyclic agents. Am J Med 2000; 108:2-8.
62. Psychotropic drugs and myocardial infarction: cause for or caused by panic? [editorial] Lancet 1992; 340:1069-71.
63. Haines A P, Imeson J D, Meade T W. Phobic anxiety and ischaemic heart disease. BMJ 1987; 295:297-9.
64. Weissman M M, Markowitz J S, Ouellete R, Greenwald S, Kahn J P. Panic disorder and cardiovascular/cerebrovascular problems: results from a community survey. Am J Psychiatry 1990; 147:1504-8.
65. Kaplan J R, Pettygerson K, Manuck S B, Olsson G. Role of sympathetoadrenal medullary activation in the initiation and progression of atherosclerosis. Circulation 1991; 94(Suppl VI):123-32.
66. Barefoot J C, Williams R B. Antidepressant and the risk of myocardial infarction. Am J Med 2000; 108:87-8.
67. Reznik I, Rosen Y, Rosen B. An acute ischaemic event associated with the use of venlafaxine: a case report and proposed pathophysiological mechanism. J Psychopharmacol 1999; 13:193-5.
68. Ketch J, Herd A, Ludwig L. ST segment elevations without myocardial infarction in a patient on clozapine. Am J Emerg Med 1996; 1:111-2.
69. Perrier A, Martin P V, Favre H, Muller A F, Urban P, Chevrolet J C. Very severe self-poisoning lithium carbonate intoxication causing a myocardial infarction. Chest 1991; 100:863-5.
70. Hollister L E, Muller Oerlinghausen B, Richels K, Shader R I. Clinical uses of benzodiazepines. J Clin Psychopharmacol 1993; 13(6 Suppl1):1S-16S.
71. Buckley N A, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf 2000; 23:215-28.
72. Killian J G, Kerr K, Lawrence C, Celermajer D S. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999; 354:1841-5.
73. Glue P, Banfield C. Psychiatry, psychopharmacology and P-450s. Hum Psychopharmacol 1996; 11:97-114.
74. Idle R J. Correspondence: The heart of psychotropic drug therapy. Lancet 2000; 355:1445.
75. Thum T, Borlak J. Gene expression in distinct regions of the heart. Lancet 2000; 355:979-83.
76. Yue Q Y, Svensson J O, Alm C, Sjoqvist F, Sawes J. Interindividual and inter ethnic differences in the demethylation and glucuronidation of codeine. Br J Clin Pharmacol 1989; 28:629-37.
77. Venning G E. Validity of anecdotal reports of suspected adverse drug reactions: the problems of false alarms. Br J Psychiatry 1982; 284:249-52.
78. Drici M D, Wang W X, Liu X K, Woosley R L, Flockhart D A. Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol 1998; 18:477-81.