Cardiologic side effects of psychotropic drugs

Giuseppe Marano1, Gianandrea Traversi1, Enrico Romagnoli2, Valeria Catalano1, Marzia Lotrionte3, Antonio Abbate4, Giuseppe Biondi-Zoccai5, Marianna Mazza1

1Department of Neurosciences, Institute of Psychiatry, Università Cattolica del Sacro Cuore, Rome 00168, Italy
2Division of Cardiology, Policlinico Casilino, Rome 00168, Italy
3Institute of Cardiology, Università Cattolica del Sacro Cuore, Rome 00168, Italy
4VCU Pauley Heart Center, Medical College of Virginia, Richmond, 23298 Virginia, USA
5Division of Cardiology, University of Modena and Reggio Emilia, Modena 41121, Italy

Abstract

Psychotropic drugs can produce cardiovascular side effects associated with a degree of cardiotoxicity. The coexistence of a heart disease complicates the management of mental illness, can contribute to a reduced quality of life and a worse illness course. The co-occurrence of psychiatric disorders in cardiac patients might affect the clinical outcome and morbidity. Moreover, the complex underlying mechanism that links these two conditions remains unclear. This paper discusses the known cardiovascular complications of psychotropic drugs and analyzes the important implications of antidepressive treatment in patients with previous cardiac history.

Keywords: antidepressants; antipsychotics; arrhythmia; cardiotoxicity; cardiovascular system; psychiatric disorders

1 Introduction

The World Health Organization has defined an adverse drug reaction as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”. Edwards provided a more recent definition: “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product”.[1] In general, adverse drug reactions are conditions that might depend on a sufficiently augmented administration (75%) or types of immunological reactions (25%).[2]

An extensive body of researches have reported cardiovascular mortality in patients suffering from psychiatric illness.[3] Some types of antidepressants and antipsychotics have various cardiovascular side effects that can lead to cardiovascular complications, especially cardiac arrhythmias, which in some cases have resulted in death of people with no previous cardiac history. Furthermore, the fact that psychotropic drugs have various cardiovascular effects may also negatively affect clinical outcome of cardiac patients. Based on these arguments, it has been developed a novel line of antidepressants which produce fewer cardiovascular side effects.[3] Furthermore, a meta-analysis conducted by Mazza and coworkers suggests that patients with acute coronary syndromes show lower re-hospitalization rates when they receive treatment with selective serotonin reuptake inhibitors (SSRIs).[4] The SSRIs represent a promising, effective and tolerable treatment that could improve quality of life for patients with acute coronary syndromes and their families.

For managing depression attributed to adverse effects of medications, determining whether or not the agent in question is actually necessary and whether alternative approaches for treatment are available is important. In most, the initial step in managing depression thought to be related to adverse drug effects is withdrawal of the agent held to be the main cause.[3]

No drug can be completely safe and the estimation of the probability that a drug caused an adverse clinical event is usually entrusted to clinical judgment. The occurrence of adverse drug reaction is a price that a patient has to pay in order to obtain therapeutic advantages benefits. In this way
the physician have to be very scrupulous in the prescription management, and it is necessary to pay attention to undesirable reaction ensuring that patients receive therapeutic benefits. The potential risk of unwanted and unexpected drug reactions can be so significant that caution should be exercised when patients receiving medications. The judgment of the physician is continuously needed, health professionals need to be aware of the evidence pertaining to differences in side effects, clinical characteristics of the patient should be evaluated withdrawing all unsuitable medications and attention should be paid to the knowledge of possible undesirable reaction in order to practice preventive strategies might help to reduce the risk of adverse drug reactions.

2 Cardiovascular disease: mortality and comorbidity

Cardiovascular disease indicates a wide class of disorders that involve the heart and, sometimes, the blood vessels. Cardiovascular disease includes conditions such as aneurysm, angina, atherosclerosis, cerebrovascular disease, congenital heart defects, coronary artery disease, heart attack, myocarditis, peripheral vascular disease and stroke. Risk factors for developing cardiovascular disease include alcohol intake, diet, dyslipidemia, hypertension, hyperglycemia, obesity, physical activity, psychosocial factors and smoking habits. Other non-modifiable risk factors are age, biological sex, genetic background and previously accumulated risks.[5]

Most countries have to face high and increasing rates of cardiovascular disease, which represents a major cause of death and disability.[6] The prevalence of depression is between 8% and 12% in the world[7,8] and, by the year 2020, it is projected to reach the second place of the biggest disease burden following cardiovascular disease.[8,9] On the other hand, 20%–40% of cardiac patients were identified as being even more seriously affected by depression.[10,11] For patients who suffer from depression the risk of developing a myocardial infarction are quite common.[8,12] In 2009, according to the American Heart Association the socioeconomic burden of healthcare resources for cardiovascular disease would amounts to $475.3 billion.

It has been reported a link between people affected by mental illness and increased levels of mortality. In case of people with schizophrenia, it is estimated that they are more likely to die with an increased mortality rate equal to an average loss of 25 years form the expected lifespan.[13–15] On the other hand, in bipolar patients established coronary heart disease signifies a higher risk for subsequent coronary heart disease mortality, in particular 1.9 times greater for men and 2.6 times greater for women in comparison with subjects without a comorbid cardiovascular disorder.[14,16] The key to face this question could be the presence of modifiable risk factors that contribute to cardiovascular disease, and a decline in cardiovascular burden across patients could be attributed to risk-factor modification. There is increasing awareness that people affected by mental illness tend to develop a cardiovascular disorder, thus the physician should carefully evaluate clinical conditions and provide a refine treatment to match the intensity of treatment to patients’ risk for future adverse cardiovascular events.[14,16]

There is a growing body of evidence that people affected by psychiatric disorders are more likely to suffer from cardiovascular disease.[5,17–20] Among all the potential comorbidities, depression represents the psychiatric condition that is associated with cardiovascular disease at higher prevalence, because depression might have an etiological as well as a prognostic role.[5] The coexistence of a heart disease complicates the management of depression and can contribute to a reduced quality of life and a worse illness course. In depressed patients the identification of a comorbid disorder should trigger careful clinical assessment.

Moreover, the complex underlying mechanism that links these two conditions remains unclear. Although the association between depression and cardiovascular disease has been recognized, it is difficult to establish whether the illness is a real medical comorbidity, a harmful side effect of medications, or a combination of both, and the precise nature of the relationship among cardiovascular disease, mortality and mental illness is not clearly delineated. It is possible that an accumulation of risk factors may have a powerful impact on those patients with serious and persistent psychiatric disorders and, potentially, leading to the development of secondary diagnoses.[21] However, it has also been hypothesized that the co-occurrence of cardiovascular disease, mortality and mental illness might be worsened by the presence of other factors such as genetic predisposition, psychotropic drugs and healthcare system.[5]

In clinical psychiatric practice, physicians should evaluate patients suffering from depression for the coexistence of cardiovascular disease. Like this, the correct diagnosis of a comorbid cardiovascular disease can prevent to expose a patient to the progression of the disorder using appropriate pharmacologic and psychological interventions in order to ensure the improvement of prognosis.

3 Sex differences in psychotropic drug-induced side effects

Few studies have examined how sex might affect side effects of psychotropic medications. Being female has been
identified as a risk factor in the development of side effects due to psychotropic drugs.\[2\] There are some studies suggesting that women show a higher prevalence (50%–75%) in the occurrence of adverse drug reaction which can jeopardize health.\[22\]

Body mass index, drug metabolism and body fluid constituents were shown to have an involvement in the development of side effects.\[2,22\] Different circumstances were studied prospectively for factors which might influence the side effects of psychotropic drugs such as gastric emptying rates and menstrual cycle,\[24–26\] hepatic drug metabolism,\[27–32\] and renal drug clearance.\[33–36\]

Beyond adverse drug reaction, patients experience with a low quality of life also contribute to patient adherence, thus tolerability profile was also examined. At present, most published studies have focused mainly on demonstrating a parameter that should not be overlooked. The occurrence of adverse drug reaction which can jeopardize health.\[2,22\]

Patients treated with MAOIs occasionally appeared to experience “spontaneous” hypertensive episode without eating foods rich in tyramine.\[56\] Sometimes this cardiovascular event was transient, but seldom the hypertensive episodes could lead to hypertensive crisis.\[55,57,58\]

TCAs are one of the oldest classes of antidepressant, most commonly prescribed as the standard treatment for depression before the introduction of SSRIs that cause fewer side effects. At present, TCAs are not considered first-line medications for psychiatric disorders. The question of using them is controversial because of the unresolved issue of possible sudden unexplained cardiac fatalities. Nevertheless, TCAs are still prescribed to people for whom SSRIs are ineffective or inappropriate.\[3\] TCAs have significantly high rate of serious cardiovascular side effects and toxicity in patients without previous cardiovascular disease.\[3,59–62\] The major side effects include heart rate increase, blood pressure abnormalities and slight prolongation of the intraventricular conduction time. Serious conduction alterations, including right and left bundle-branch block or partial or complete atrioventricular block, occur at high or toxic plasma levels and are reflected in electrocardiogram (ECG) as prolonged PR, QRS and QT intervals and T-wave flattening or inversion.\[63–66\] TCAs may slow electrical conduction inducing a prolongation of the electrical impulse\[67,68\] and therefore they have a higher risk of causing arrhythmias, especially in individuals with conduction disease.\[67,68\] It has been documented in literature that TCAs may also behave as class 1A antiarrhythmics reducing intraventricular conduction velocity and increasing collateral blood circulation.\[69–71\]

This antiarrhythmic effect at therapeutic plasma level is responsible for extremely high plasma levels that cause arrhythmias and heart block as well as the high rate of mortality after TCAs’ overdose. This case must be considered when patients are already taking type 1 antiarrhythmics, because the dosage may need to be changed. Moreover, patients following antiarrhythmic drug therapy would require a close ECG monitoring. The therapeutic role of TCAs for children needs to be seriously
weighed against lethality. There have been a number of case reports of sudden unexplained death occurring in children stable on TCAs.\textsuperscript{72–74} Any suspected overdose should be treated as an emergency, it is a significant cause of fatal drug poisoning due to TCAs’ cardiovascular toxicity.\textsuperscript{[3]}

TCAs tend to cause a combination of troubling adverse effects that are more likely to affect cardiovascular parameters. Moreover, TCAs increase a potential cardiac risk and should be taken with great scrupulousness in individuals affected by cardiovascular disease. If physicians do prescribe TCAs, it is important to be fully informed of potential cardiovascular complications.\textsuperscript{[3]}

5 Cardiac and circulatory adverse effects of new antidepressants

SSRIs have largely replaced TCAs as the drug of choice in the treatment of mental illness, mainly because of their favorable side effect profile. The antidepressants of this class are therapeutically similar, but important pharmacokinetic differences exist among these drugs in terms of metabolism and hepatic clearance. Despite a favorable clinical profile SSRIs still produce side effect with less frequency and intensity than other antidepressants. The major difference between SSRIs and TCAs is a significant anticholinergic effect as well as low cardiotoxicity.\textsuperscript{[3]} In fact, SSRIs are now widely prescribed in preference to TCAs because of their lower side effect profile and reduced toxicity after overdose. To date, only two SSRIs overdose death have been reported in literature, one involved the ingestion of fluoxetine\textsuperscript{[75]} and the other implied the use of citalopram.\textsuperscript{[76,77]} Side-effects profile for the SSRIs shows greater similarities to each other than differences (Table 1). SSRIs induce significantly less anti-cholinergic, anti-histaminergic and cardiototoxic side effects than TCAs. The most common cardiac side effects are a mild bradycardia, orthostatic hypotension and abnormalities in the electrical activity of the heart such as QRS lengthening or prolonged QT interval.\textsuperscript{[77,78]} SSRIs may also exert a direct vasoconstrictive effect leading to a myocardial ischemia known as Prinzmetal’s angina.\textsuperscript{[77,79]} Moreover, accounting for the vasoconstrictive effects of SSRIs, extreme caution should be exercised in the use of SSRIs treatment in patients who are at increased risk for hemorrhagic and vasoconstrictive diseases.

| Table 1. Licensed indications, mechanism of action and comparative tolerability and side effects of SSRIs.\textsuperscript{[77]} |
|---------------------------------------------------------------|
| **FDA approved year** | **FDA therapeutic indications** | **Mechanism of action** | **Cardiovascular profile** |
|----------------------|---------------------------------|--------------------------|---------------------------|
| Citalopram           | 1998 Major depressive disorder  | A highly selective and potent serotonin reuptake inhibitor | Uncommon (≥ 1/1000 to <1/100): bradycardia, orthostatic hypotension, tachycardia; Rare (≥ 1/10000 to <1/1000): atrial fibrillation, bundle branch block, cardiac arrest, hypertension, myocardial infarction, phlebitis, transient ischemic attacks, stroke |
| Escitalopram         | 2002 Major depressive disorder; generalized anxiety disorder | More selective serotonin reuptake inhibitor than citalopram | Uncommon (≥ 1/1000 to <1/100): tachycardia; Rare (≥ 1/10000 to <1/1000): bradycardia, orthostatic hypotension |
| Fluoxetine           | 1987 Bulimia nervosa; major depressive disorder; obsessive compulsive disorder; panic disorder; premenstrual dysphoric disorder | Potent and selective inhibitor of serotonin reuptake with antidepressant, antiobsessional and antibulimic effects | Uncommon (≥ 1/1000 to <1/100): junctional rhythms, mild bradycardia, sinus tachycardia, ventricular trigeminy; Rare (≥ 1/10000 to <1/1000): ECG abnormalities, thrombophlebitis |
| Fluvoxamine          | 1993 Major depressive disorder; obsessive compulsive disorder | A selective serotonin reuptake inhibitor with affinity for the serotonin transporter over the norepinephrine transporter | Uncommon (≥ 1/1000 to <1/100): ST segment changes, atrioventricular and supraventricular blockade; Rare (≥ 1/10000 to <1/1000): coronary heart disease, embolus, pericarditis, phlebitis, pulmonary infarction, stroke |
| Paroxetine           | 1992 Generalized anxiety disorder; major depressive disorder; obsessive compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social anxiety disorder | The most potent inhibitor of the reuptake of serotonin | Uncommon (≥ 1/1000 to <1/100): hypertension, syncope, tachycardia; Rare (≥ 1/10000 to <1/1000): angina pectoris, bradycardia, congestive heart failure, hypotension, myocardial infarction, thrombophlebitis, vascular headache |
SSRIs interfere with serotonin accumulation in platelets and SSRI treatment (but not TCAs’ treatment) normalizes elevated indices of platelet activation and aggregation in patients with depression and ischemic heart disease. The antipllatelet effect of SSRIs is neither associated with antidepressant effect nor does resolution of depression immediately normalize increased platelet activity. The antiplatelet effect of SSRIs may reduce risk of future ischemic cardiovascular events. SSRI-treated patients have a significantly low rate of myocardial infarction than the non-SSRI-treated patients. This lower myocardial infarction rate may not simply be due to reduced psychiatric symptoms; for instance, patients whose anxiety is reduced by anxiolytic medications do not have a reduced rate of myocardial infarction.

In conclusion, the use of TCAs and structurally related antidepressants should be limited in cardiac patients because of the myriad of side effects of these medications on the cardiovascular system, including orthostatic hypotension, tachycardia, reduction in heart rate variability and slowing of intraventricular conduction. These antidepressants should never be prescribed for patients with bundle branch block. As might be expected, examination of prescription has revealed an increased risk of myocardial infarction with administration of TCAs in comparison to SSRIs and atypical antidepressants. MAOIs are generally free of effects on cardiac conduction, but, like TCAs, may cause postural hypotension. Because of their fewer potential adverse effects on the cardiovascular system and the lack of lethality from an overdose, pharmacotherapeutic treatments with SSRIs may offer significant advantages in depressed or anxious patients affected by cardiovascular disease.

6 Cardiac and circulatory adverse effects of antipsychotics

Antipsychotic medications are used to treat psychotic symptoms and other mental and emotional conditions. The first class of these drugs was introduced in the 1950s and was known as typical antipsychotics. The early antipsychotic medications often have unpleasant side effects, thus researchers continue their search for better drugs and developed the second generation called atypical antipsychotics. Important antipsychotic-induced cardiovascular effects include cardiac arrhythmia and cardiac arrest, whereas orthostatic hypotension is more common in elderly patients. The combination of antipsychotic-induced orthostatic changes and age-related loss of postural reflexes leads to an increased risk of falls in older adults. Therefore, orthostatic hypotension episodes are particularly dangerous at night, when the older patients awaken to urinate and gets out of bed quickly.

A further adverse health outcome in the profile of antipsychotic drugs is tachycardia that seems to occur primarily as result of the anticholinergic properties of antipsychotics. Epidemiological studies provide evidence that antipsychotics increase the risk of sudden cardiac death. Specifically, certain antipsychotics can induce prolongation of the QT interval, that can potentate a lethal ventricular arrhythmia. Among the antipsychotic drugs, ziprasidone is associated with the greatest QT prolongation.

In addition to their effect on cardiac conduction, antipsychotic medications do not have extremely negative effects in case of overdose: clozapine induces tachycardia, olanzapine and quetiapine do not determine tachycardia, and risperidone shows no significant symptoms in the 66% of the cases, but could provoke sudden death.

However, patients with pre-existing cardiovascular disease should be carefully evaluated before they begin any antipsychotic treatment. In particular, extreme caution is required in prescribing drugs with anticholinergic properties or those that produce orthostatic hypotension.

7 Behavioral cardiology: the impact of the psychological on cardiovascular well-being

Psychological stress can have serious negative effects on well-being and plays a large role in several diseases such as diabetes, cancer, immunological disorders and cardiovascular diseases are another areas where stress could have a negative effect. In this context, expressive and overwhelmingly significant body of evidences have been provided by the INTERHEART study that has measured whether psychosocial stress can be considered as a risk factor associated with myocardial infarction. In this analysis, psychosocial stress has placed in the third place among cardiovascular risk factor and one-third of the total risk is attributable to this modifiable factor.
there is a distinct connection between depression and increased risk of cardiovascular disease. Depression may be considered a prognostic factor in patients affected by cardiovascular disorders and could be useful in risk stratification, with the fact that the presence of depression is threefold higher among cardiovascular patients.\cite{90,92-97}

Milani and Lavie conducted a study to evaluate the effect of cardiac rehabilitation on depression.\cite{98} All patients who received cardiac rehabilitation experienced a sensible reduction of depressive symptoms severity (from 17% to 6%) and mortality.\cite{98} In 2009, Milani and Lavie found that, in the context of a structured cardiac rehabilitation, the exercise training improves levels of psychosocial stress and has a strong influence on the incidence of heart disease and overall mortality, that is 60% lower compared with control subjects.\cite{99} In a more recent study, Milani et al.\cite{100} performed a research to examine the influence on exercise training in patients suffered from coronary heart disease. They identified positive changes in depression status with a symptom reduction by 40% associated with a decrease in mortality by 59% in comparison with patients not undergoing rehabilitation.

Although the importance of psychological stress in the development of cardiovascular disease has been mainly valued in presence of depressive symptoms, other behavioral factors including anxiety and hostility have provided clear and convincing evidence that contribute significantly to the expression of cardiovascular disorders.\cite{90,93,101-103} Among patients with heart disease, anxiety syndromes appear to be associated with a higher risk of cardiovascular disorders.\cite{90,104-109}

Anxiety and cardiovascular disease frequently coexist, and there is evidence to suggest that anxiety may be an independent risk factor for cardiac morbidity and mortality, in addition to leading to poorer outcomes.\cite{90} Cardiac rehabilitation and exercise training significantly improve anxiety’s levels up to half their rate.\cite{106} In a recent meta-analytic review, Herring et al.\cite{110} individuated that patients who exercise reported fewer anxiety symptoms, lower levels of stress and improved their prognosis. On the other hand, hostility may be an indirect cause of the high rate of cardiovascular problems, because leads to a fivefold increased risk of developing cardiovascular disease.\cite{90,111-115}

Studies have reported that cardiac patients with high levels of hostility subsequently showed significant improvement in cardiac efficiency after exercise training.\cite{90,115,116}

To date, a causal relationship and the pathophysiological mechanisms underlying psychological stress and cardiovascular health have not yet well delineated, whereby psychosocial conditions personality factors and character traits contribute to a higher frequency of adverse health behavior, such as poor diet, physical activity, height weight and smoking, and direct pathophysiological mechanisms, such as imbalance in the autonomic nervous system, neuroendocrine activation, endothelial dysfunction, vasoconstriction and stimulation of platelet function.\cite{90} Therefore, cardiac rehabilitation program brings advantages to cardiovascular health involving mechanisms not entirely identified, but likely multifactorial.\cite{90}

Although SSRIs appear to be the safest antidepressant medication for use in cardiac patients, there is data suggesting that exercise training is associated with reduced morbidity and mortality.\cite{90} The effectiveness of behavioral intervention for cardiac patients needs to be evaluated in clinical setting and, maybe, an exercise training program should be recommended for cardiac patients with depression and high psychological distress prior to going on a treatment with psychotropic drugs.

### 8 Conclusions

Antidepressants are one of the most-prescribed class of drugs in the United States.\cite{117} MAOIs, TCAs and antipsychotics could be both effective for the treatment of mental illness, but their cardiovascular side effects and sometimes toxicity in overdose show many disadvantages. On the basis of a cardiovascular profile with fewer adverse reactions, the SSRIs are generally well-tolerated agents and should therefore be the preferred choice of the treatment of most patients with comorbid cardiovascular disease.

An important topic is related to the diagnosis of psychiatric disorders in the face of significant comorbidity from medical conditions such as cardiovascular disease. Depression occurs in most cases as a component, complication or consequence of comorbid medical disease. Depression itself could represent a risk factor for cardiovascular events as well as stroke, coronary heart disease and early death.\cite{12,77,117-121} Therefore, it has also been addressed the issue of determining whether a condition is related to the nature of the underlying illness or to the nature of the treatment given.

“The right drug for the right patient”\cite{112,123} is the assertion to whom health professionals should be inspired in their learning motives, their comprehensive ability and their clinical activity. Clinicians should be vigilant in conducting a rigorous assessment for the development of adverse effects and providing monitoring recommendations before beginning psychopharmacological treatment. Physicians have to take into account their knowledge about cardiovascular profile of psychotropic drugs when screening a patient for physical or mental problems. In case of medical
comorbidity, clinician should provide a plan for alternative treatment and monitoring of the patient’s well being and should determine the most effective approach developing indications for drug prescription on the basis of predictive risk profile and potential adverse drug effects.\textsuperscript{[3,77]} Moreover, clinicians have also to pay a particular attention to psychotropic drugs combination when patients are affected by cardiovascular disease. Drugs interaction can lead to cardiovascular complications, thus the physician has to focus attention on assessing and monitoring cardiac status in patients treated with psychotropic drugs.\textsuperscript{[77]}

Additional studies to explore the cellular and molecular basis of the cardiac profile of psychotropic drugs in the etiology or clinical manifestations as well as others are warranted. These may lead to new forms of prevention as well as treatment.\textsuperscript{[3,77]}

References

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. \textit{Lancet} 2000; 356: 1255–1259.
2. Haack S, Seeringer A, Thürmann PA, \textit{et al.} Sex-specific differences in side effects of psychotropic drugs: genes or gender? \textit{Pharmacogenomics} 2009; 10: 1511–1526.
3. Pacher P, Kocsis EM. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? \textit{Curr Pharm Des} 2004; 10: 2463–2475.
4. Mazza M, Lotrionte M, Biondi-Zoccai G, \textit{et al.} Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: evidence from a meta-analysis. \textit{J Psychopharmacol} 2010; 24: 1785–1792.
5. Mackin P. Cardiac side effects of psychiatric drugs. \textit{Hum Psychopharmacol} 2008; 23: 3–14.
6. Murray C, Lopez A. Alternative visions of the future: projecting mortality and disability 1990–2020. In \textit{The Global Burden of Disease}; Murray C, Lopez A, Eds.; Harvard University Press: Cambridge, 1996; 325–397.
7. Andrade L, Caraveo-Anduaga JJ, Berglund P, \textit{et al.} The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. \textit{Int J Methods Psychiatr Res} 2003; 12: 3–21.
8. Kemp AH, Quintana DS, Gray MA, \textit{et al.} Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. \textit{Biol Psychiatry} 2010; 67: 1067–1074.
9. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. \textit{Lancet} 1997; 349: 1498–1504.
10. Carney RM, Rich MW, Tevelde A, \textit{et al.} Major depressive disorder in coronary artery disease. \textit{Am J Cardiol} 1987; 60: 1273–1275.
11. Gonzalez MB, Snyderman TB, Colket JT, \textit{et al.} Depression in patients with coronary artery disease. \textit{Depression} 1996; 4: 57–62.
12. Pratt LA, Ford DE, Crum RM, \textit{et al.} Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. \textit{Circulation} 1996; 94: 3123–3129.
13. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. \textit{Br J Psychiatry} 2000; 177: 212–217.
14. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. \textit{Prev Chronic Dis} 2006; 3:A42.
15. Osborn DP, Levy G, Nazareth I, \textit{et al.} Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. \textit{Arch Gen Psychiatry} 2007; 64: 242–249.
16. Osby U, Brandt L, Correa N, \textit{et al.} Excess mortality in bipolar and unipolar disorder in Sweden. \textit{Arch Gen Psychiatry} 2001; 58: 844–850.
17. Enger C, Weatherby L, Reynolds RF, \textit{et al.} Serious cardiovascular events and mortality among patients with schizophrenia. \textit{J Nerv Ment Dis} 2004; 192: 19–27.
18. Goff DC, Sullivan LM, McEvoy JP, \textit{et al.} A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. \textit{Schizophr Res} 2005; 80: 45–53.
19. Frasure-Smith N, Lespérance F. Recent evidence linking coronary heart disease and depression. \textit{Can J Psychiatry} 2006; 51: 730-737.
20. Mackin P, Bishop DR, Watkinson HM. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. \textit{BMC Psychiatry} 2007; 7: 28.
21. Marano G, Harnic D, Lotrionte M, \textit{et al.} Depression and the cardiovascular system: increasing evidence of a link and therapeutic implications. \textit{Expert Rev Cardiovasc Ther} 2009; 7: 1123–1147.
22. Martin RM, Biswas PN, Freemantle SN, \textit{et al.} Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. \textit{Br J Clin Pharmacol} 1998; 46: 505–511.
23. Anderson GD. Gender differences in pharmacological
response. *Int Rev Neurobiol* 2008; 83: 1–10.

24 Hutson WR, Roehrkasse RL, Wald A. Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* 1989; 96: 11–17.

25 Kashuba AD, Nafziger AN. Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. *Clin Pharmacokinet* 1998; 34: 203–218.

26 Stahl SM. Basic psychopharmacology of antidepressants, part 1: Antidepressants have seven distinct mechanisms of action. *J Clin Psychiatry* 1998; 59: 5–14.

27 Pollock BG. Gender differences in psychotropic drug metabolism. *Psychopharmacol Bull* 1997; 33: 235–241.

28 Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. *Int J Clin Pharmacol Ther* 1999; 37: 529–547.

29 Prior TI, Baker GB. Interactions between the cytochrome P450 system and the second-generation antipsychotics. *J Psychiatry Neurosci* 2003; 28: 99–112.

30 Schwartz JB. The influence of sex on pharmacokinetics. *Clin Pharmacokinet* 2003; 42: 107–121.

31 Parkinson A, Mudra DR, Johnson C, *et al*. The effects of gender, age, ethnicity, and liver cirrhosis on cytochrome P450 enzyme activity in human liver microsomes and inducibility in cultured human hepatocytes. *Toxicol Appl Pharmacol* 2004; 193: 193–209.

32 Aichhorn W, Whitworth AB, Weiss EM, *et al*. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? *Drug Saf* 2006; 29: 587–598.

33 Gross JL, Friedman R, Azevedo MJ, *et al*. Effect of age and sex on glomerular filtration rate measured by 51Cr-EDTA. *Braz J Med Biol Res* 1992; 25: 129–134.

34 Schuetz EG, Furuya KN, Schuetz JD. Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. *J Pharmacol Exp Ther* 1995; 275: 1011–1018.

35 Arnold LM, Strakowski SM, Schwiers ML, *et al*. Sex, ethnicity, and antipsychotic medication use in patients with psychosis. *Schizophr Res* 2004; 66: 169–175.

36 Salokangas RK. Gender and the use of neuroleptics in schizophrenia. *Schizophr Res* 2004; 66: 41–49.

37 Kasper S. First-episode schizophrenia: the importance of early intervention and subjective tolerability. *J Clin Psychiatry* 1999; 23: 5–9.

38 Naber D, Karow A. Good tolerability equals good results: the patient’s perspective. *Eur Neuropsychopharmacol* 2001; 11: 391–396.

39 Awad AG, Voruganti LN. New antipsychotics, compliance, quality of life, and subjective tolerability—are patients better off? *Can J Psychiatry* 2004; 49: 297–302.

40 Barbui C, Nosè M, Bindman J, *et al*. Sex differences in the subjective tolerability of antipsychotic drugs. *J Clin Psychopharmacol* 2005; 25: 521–526.

41 Hamilton JA, Halbreich U. Special aspects of neuropsychiatric illness in women: with a focus on depression. *Annu Rev Med* 1993; 44: 355–364.

42 Frackiewicz EJ, Sramek JJ, Cutler NR. Gender differences in depression and antidepressant pharmacokinetics and adverse events. *Ann Pharmacother* 2000; 34: 80–88.

43 Hildebrandt MG, Steyerberg EW, Stage KB, *et al*. Are gender differences important for the clinical effects of antidepressants? *Am J Psychiatry* 2003; 160: 1643–1650.

44 Havercamp W, Breithardt G, Camm AJ, *et al*. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. *Eur Heart J* 2000; 21: 1216–1231.

45 Yap YG, 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: 1158–1159.

46 Agelink MW, Majewski T, Wurthmann C, *et al*. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. *J Clin Psychopharmacol* 2001; 21: 8–13.

47 Czekalla J, Beasley CM Jr, Della MA, *et al*. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. *J Clin Psychiatry* 2001; 62: 191–198.

48 Bailey MS, Curtis AB. The effects of hormones on arrhythmias in women. *Curr Womens Health Rep* 2002; 2: 83–88.

49 Harrigan EP, Miceli JJ, Anziano R, *et al*. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol* 2004; 24: 62–69.

50 Laakso M, Aberg A, Savola J, *et al*. Diseases and drugs causing prolongation of the QT interval. *Am J Cardiol* 1987; 59: 862–865.

51 Kassotis J, Costea C, Bedi AK, *et al*. Effects of aging and gender on QT dispersion in an overtly healthy population. *Pacing Clin Electrophysiol* 2000; 23: 1121–1126.

52 Drici MD, Clément N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf* 2001; 24: 575–585.
53. Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that may prolong the QT interval. *J Clin Psychopharmacol* 2003; 23: 197–200.

54. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. *J Cardiovasc Electrophysiol* 1998; 9: 655–664.

55. Wimbisicus M, Kostenko O, Malone D. MAO inhibitors: risks, benefits, and lore. *Cleve Clin J Med* 2010; 77: 859–882.

56. Lavin MR, Mendelowitz A, Kronig MH. Spontaneous hypertensive reactions with monoamine oxidase inhibitors. *Biol Psychiatry* 1993; 34: 146–151.

57. Linet LS. Mysterious MAOI hypertensive episodes. *J Clin Psychiatry* 1986; 47: 563–565.

58. Fallon B, Foote B, Walsh BT, et al. 'Spontaneous' hypertensive episodes with monoamine oxidase inhibitors. *J Clin Psychiatry* 1988; 49: 163–165.

59. Burckhardt D, Raeder E, Müller V, et al. Cardiovascular effects of tricyclic and tetracyclic antidepressants. *JAMA* 1978; 239: 213–216.

60. Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. A review. *Arch Gen Psychiatry* 1981; 38: 815–820.

61. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med* 1984; 35: 503–511.

62. Pacher P, Ungvari Z, Nanasi PP, et al. Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any? *Curr Med Chem* 1999; 6: 469–480.

63. Kantor SJ, Bigger JT Jr, Glassman AH, et al. Imipramine-induced heart block. A longitudinal case study. *JAMA* 1975; 231: 1364–1366.

64. Vohra J, Burrows G, Hunt D, et al. The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction. *Eur J Cardiol* 1975; 3: 219–227.

65. Giardina EG, Bigger JT Jr, Glassman AH, et al. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. *Circulation* 1979; 60: 1045–1052.

66. Glassman AH, Bigger JT Jr, Giardina EV, et al. Clinical characteristics of imipramine-induced orthostatic hypotension. *Lancet* 1979; 1: 468–472.

67. Giardina EG, Bigger JT Jr, Glassman AH, et al. Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch Gen Psychiatry* 1987; 44: 273–275.

68. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. *JAMA* 1993; 269: 2673–2675.

69. Bigger JT, Giardina EG, Perel JM, et al. Cardiac antiarrhythmic effect of imipramine hydrochloride. *N Engl J Med* 1977; 296: 206–208.

70. Giardina EG, Bigger JT Jr. Antiarrhythmic effect of imipramine hydrochloride in patients with ventricular premature complexes without psychological depression. *Am J Cardiol* 1982; 50: 172–179.

71. Giardina EG, Barnard T, Johnson L, et al. The antiarrhythmic effect of nortriptyline in cardiac patients with ventricular premature depolarizations. *J Am Coll Cardiol* 1986; 7: 1363–1369.

72. Biederman J. Sudden death in children treated with a tricyclic antidepressant. *J Am Acad Child Adolesc Psychiatry* 1991; 30: 495–498.

73. Riddle MA, Geller B, Ryan N. Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 1993; 32: 792–797.

74. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 390–394.

75. Kincaid RL, McMullin MM, Crookham SB, et al. Report of a fluoxetine fatality. *J Anal Toxicol* 1990; 14: 327–329.

76. Oström M, Eriksson A, Thorson J, et al. Fatal overdose with citalopram. *Lancet* 1996; 348: 339–340.

77. Fernández A, Bang SE, Srivathsan K, et al. Cardiovascular side effects of newer antidepressants. *Anadolu Kardiyl Derg* 2007; 7: 305–309.

78. Rodriguez de la Torre B, Dreher J, Malevany I, et al. Serum levels and cardiovascular effects of tricyclic antidepressants and selective serotonin reuptake inhibitors in depressed patients. *Ther Drug Monit* 2001; 23: 435–440.

79. Frischione GL, Woznicki RM, Klesmer J, et al. Vasocostructive effects and SSRIs. *J Clin Psychiatry* 1993; 54: 71–72.

80. Kharafo J, Sekar P, Haverbusch M, et al. Selective serotonin reuptake inhibitors and risk of hemorrhagic stroke. *Stroke* 2007; 38: 3049–3051.

81. Kim DH, Daskalakis C, Whellan DJ, et al. Safety of selective serotonin reuptake inhibitor in adults undergoing coronary artery bypass grafting. *Am J Cardiol* 2009; 103: 1391–1395.

82. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; 28: 345–367.

83. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician* 2010; 81: 617–622.

84. Mehtonen OP, Aranko K, Mäkikonen L, et al. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatr Scand* 1991; 84: 58–64.
Buckley NA, Whyte IM, Dawson AH. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. *J Toxicol Clin Toxicol* 1995; 33: 199–204.

Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. *Clin Ther* 2002; 24: 21–37.

Ravin DS, Levenson JW. Fatal cardiac event following initiation of risperidone therapy. *Ann Pharmacother* 1997; 31: 867–870.

Capel MM, Colbridge MG, Henry JA. Overdose profiles of new antipsychotic agents. *Int J Neuropsychopharmacol* 2000; 3: 51–54.

Figueroed VM. The time has come for physicians to take notice: the impact of psychosocial stressors on the heart. *Am J Med* 2009; 122: 704–712.

Lavie CJ, Milani RV, O’Keefe JH, et al. Impact of exercise training on psychological risk factors. *Prog Cardiovasc Dis* 2011; 53: 464–470.

Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 953–962.

Lespérance F, Frasure-Smith N, Talajic M, et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 2002; 105: 1049–1053.

Das S, O’Keefe JH. Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health. *Curr Hypertens Rep* 2008; 10: 374–381.

Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; 118: 1768–1775.

Rutledge T, Vaccarino V, Johnson BD, et al. Depression and cardiovascular health care costs among women with suspected myocardial ischemia: prospective results from the WISE (Women’s Ischemia Syndrome Evaluation) Study. *J Am Coll Cardiol* 2009; 53: 176–183.

Whooley MA. To screen or not to screen? Depression in patients with cardiovascular disease. *J Am Coll Cardiol* 2009; 54: 891–893.
blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. *J Am Med Assoc* 1959; 169: 1286–1296.

112 Knox SS, Adelman A, Ellison RC, *et al.* Hostility, social support, and carotid artery atherosclerosis in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Cardiol* 2000; 86: 1086–1089.

113 Iribarren C, Sidney S, Bild DE, *et al.* Association of hostility with coronary artery calcification in young adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. *JAMA* 2000; 283: 2546–2551.

114 Yan LL, Liu K, Matthews KA, *et al.* Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA* 2003; 289: 2138–2148.

115 Lavie CJ, Milani RV. Prevalence of hostility in young coronary artery disease patients and effects of cardiac rehabilitation and exercise training. *Mayo Clin Proc* 2005; 80: 335–442.

116 Lavie CJ, Milani RV. Impact of aging on hostility in coronary patients and effects of cardiac rehabilitation and exercise training in elderly persons. *Am J Geriatr Cardiol* 2004; 13: 125–130.

117 Smoller JW, Allison M, Cochrane BB, *et al.* Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. *Arch Intern Med* 2009; 169: 2128–2139.

118 Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993; 270: 1819–1825.

119 Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995; 91: 999–1005.

120 Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation* 1996; 93: 1976–1980.

121 Penninx BW, Beekman AT, Honig A, *et al.* Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001; 58: 221–227.

122 Van Putten T, May PR, Marder SR. Response to antipsychotic medication: the doctor's and the consumer's view. *Am J Psychiatry* 1984; 141: 16–19.

123 Uçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. *World Psychiatry* 2008; 7: 58–62.