Antidepressants and cardiovascular adverse events: A narrative review

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Review Article

Abstract

BACKGROUND: Major depression or deterioration of previous mood disorders is a common adverse consequence of coronary heart disease, heart failure, and cardiac revascularization procedures. Therefore, treatment of depression is expected to result in improvement of mood condition in these patients. Despite demonstrated effects of anti-depressive treatment in heart disease patients, the use of some antidepressants have shown to be associated with some adverse cardiac and non-cardiac events. In this narrative review, the authors aimed to first assess the findings of published studies on beneficial and also harmful effects of different types of antidepressants used in patients with heart diseases. Finally, a new categorization for selecting antidepressants according to their cardiovascular effects was described.

METHODS: Using PubMed, Web of Science, SCOPUS, Index Copernicus, CINAHL, and Cochrane Database, we identified studies designed to evaluate the effects of depression and also using antidepressants on cardiovascular outcome. A 40 studies were finally assessed systematically. Among those eligible studies, 14 were cohort or historical cohort studies, 15 were randomized clinical trial, 4 were retrospective were case-control studies, 3 were meta-analyses and 2 animal studies, and 2 case studies.

RESULTS: According to the current review, we recommend to divide antidepressants into three categories based on the severity of cardiovascular adverse consequences including (1) the safest drugs including those drugs with cardio-protective effects on ventricular function, as well as cardiac conductive system including selective serotonin reuptake inhibitors, (2) neutralized drugs with no evidenced effects on cardiovascular system including serotonin–norepinephrine reuptake inhibitors, and (3) harmful drugs with adverse effects on cardiac function, hemodynamic stability, and heart rate variability including tricyclic antidepressants, serotonin antagonist and reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants.

CONCLUSION: The presented categorization of antidepressants can be clinically helpful to have the best selection for antidepressants to minimizing their cardiovascular harmful effects.

Keywords: Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressant, Antidepressants, Review

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Introduction

Major depression or deterioration of previous mood disorders is a common adverse consequence of coronary heart disease (CHD), heart failure, and cardiac revascularization procedures.[1-3] Therefore, treatment of depression is expected to result in improvement of mood condition in these patients. Despite demonstrated effects of anti-depressive treatment in heart disease patients, the use of some antidepressants have shown to be associated with some adverse cardiac and non-cardiac events that may even lead to high mortality and morbidity as well as to lower patients' survival.[4-6] Especially focusing newer antidepressants generations shows some notable adverse events (AEs) emphasizing individualize therapy to minimize these AEs.[7]

Unfortunately, in the current industrialized world, the prevalence of mood disorders has an upward trend because of economic problems, the lack of social security insurance after cardiac surgeries and also significant physical and social disabilities following disease progression. In recent published meta-analyses,

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the overall prevalence of major depression in coronary artery disease patients has been estimated 18.7% in women and 12.0% in men.[8] In patients who suffer acute myocardial infarction (MI), the prevalence of major depression ranges from 15% to 20%.[9] Those with heart failure experience higher rate of depression with a range 36%.[10] Although affected heart disease patients may remain undiagnosed with regard to the presence of depression, but most of these subjects treated with a variety of antidepressants and thus appearing side effects of these drugs is expectable in undertreated patients.

In this narrative review, the authors aimed to assess the findings of published studies on beneficial and also harmful effects of different types of antidepressants used in patients with heart diseases. Finally, a new categorization for selecting antidepressants according to their cardiovascular effects was described.

Materials and Methods

Using PubMed, Web of Science, SCOPUS, Index Copernicus, CINAHL, and Cochrane Database, we identified studies designed to evaluate the effects of depression and also using antidepressants on cardiovascular outcome (Figure 1). The study criteria for inclusion in the review were: a randomized controlled trial, cohort study, retrospective case-control study, case studies, animal experimental studies, or a meta-analysis published in a peer-reviewed journal, inclusion of patients with different types of cardiovascular disorders, and comparison of the effects of different antidepressants. The search strategy was based on the search terms "antidepressant" and "cardiovascular event." The searches were performed up to December 2014. All available English abstracts and full texts were reviewed. In initial reviewing, 275 papers met our inclusion criteria. By considering the exclusion criteria of no full-text availability, review without meta-analysis, and non-English language texts, and review articles without meta-analysis, 40 studies were finally assessed systematically. Among those eligible studies (Table 1), 14 were cohort or historical cohort studies, 15 were randomized clinical trial, 4 were retrospective were case-control studies, 3 were meta-analyses and 2 animal studies, and 2 case studies. According to drug groups evaluated, 5 groups of antidepressant medications were assessed including (1) selective serotonin reuptake inhibitors (SSRIs) (escitalopram, sertraline, citalopram, fluoxetine, paroxetine); (2) tricyclic antidepressants (TCAs) (amitriptyline, imipramine, dezipramine.); (3) serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine, sibutramine); (4) serotonin antagonist and reuptake inhibitors (SARIs) (trazodone); and (5) noradrenergic and specific serotonergic antidepressants (NaSSAs) (mirtazapine). Furthermore, the considered cardiovascular outcome included cardiac or non-cardiac related death, heart rate variability, ischemic events (MI), brain stroke, and hemodynamic instability. The data were abstracted, and differences were finally resolved by consensus.

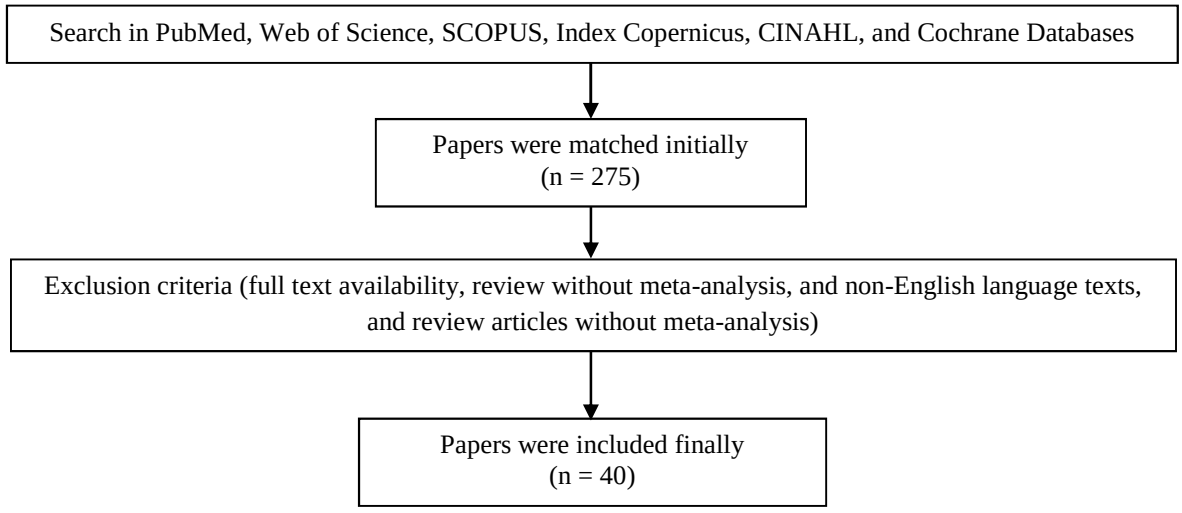

Figure 1. Process for selecting final studies

Table 1. Review of the studies on the effects of antidepressants on cardiovascular system

Author	Country	Study	Participants	End point	Finding
Rutledge et al.[10]	USA	Retrospective cohort	936 women	Depression, dietary habits, and cardiovascular events	Mechanisms linking depression to CVD is related to dietary habit
Thase et al.[11]	USA	Clinical trial	3298 on escitalopram	Cardiovascular safety profile of escitalopram	escitalopram, like other SSRIs, has a statistically significant effect on heart rate and on ECG values
Hanash et al.[12]	Denmark	Clinical trial	240 patients with CAD	Cardiovascular safety profile of escitalopram	One-year escitalopram treatment was safe and well tolerated in patients with recent ACS
Santangelo et al.[13]	Italy	Cohort study	110 the elderly	Sertraline or Citalopram and cardiovascular risk in the elderly	After 4, 6 and 12 months of treatment, we observed a reduction of the cardiovascular events
Glassman et al.[14]	USA	Clinical trial	369 patients with depression	Sertraline treatment of major depression in patients with acute MI or unstable angina	Sertraline is a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina
Wilens et al.[15]	USA	Clinical trial	187 children and adolescents	Cardiovascular adverse effects of sertraline in children and adolescents	Cardiovascular safety of sertraline at doses up to 200 mg in children and adolescents
Weeke et al.[16]	Denmark	Case-control	19,110 patients with out-of-hospital cardiac arrest	Antidepressant use and risk of out-of-hospital cardiac arrest	An association between cardiac arrest and antidepressant use was documented in both the SSRI and TCA classes of drugs
Roose et al.[17]	USA	Clinical trial	27 depressed patients with CHD	Cardiovascular effects of fluoxetine	Fluoxetine treatment was not associated with the cardiovascular effects
Yeragani et al.[18]	USA	Clinical trial	Depressed cardiac patients	effects of paroxetine and nortriptyline on long-term heart rate variability measures	nortriptyline has stronger vagolytic effects on cardiac autonomic function compared with paroxetine
Acharya et al.[19]	USA	Retrospective, cross-sectional	664 on antidepressant 472 control	Antidepressant and cardiovascular events	Favor treatment of depression with SSRIs among patients at increased cardiovascular risk
Pequignot et al.[20]	France	Cohort study	7,308 ones with no history of CAD	Antidepressants heart disease and stroke events	Depressive symptoms are associated with first fatal CHD or stroke events
Zuidersma et al.[21]	Netherland	Clinical trial	331 depressed MI-patients	Depression treatment and cardiovascular events	Receiving depression treatment increased survival
Jerrell and McIntyre[22]	USA	Retrospective cohort	14,171 children and adolescents	Cardiovascular and neurological events with antidepressant	patients were at a significantly higher risk for incident cardiovascular events when exposed to selective serotonin reuptake inhibitors and weight-inducing antidepressants
Grace et al.[23]	USA	Cohort study	661 ACS inpatients	Correlates of antidepressant use in ACS patients	Antidepressant users were more likely to be anxious and have more comorbidity, and were less likely to work full-time, whereas number of medications, age, and marital status were not related
Swenson et al.[24]	Canada	Meta-analysis	6,588 individuals with cardiovascular events	Cardiovascular events in antidepressant trials	Did not determine whether SSRIs are associated with a greater or lesser risk of cardiovascular AEs
Taylor et al.[25]	USA	Retrospective cohort	2481 depressed and/or socially isolated patients	Antidepressant medication on morbidity and mortality after MI	Use of selective serotonin reuptake inhibitors in depressed patients who experience an acute MI might reduce subsequent cardiovascular morbidity and mortality
Roose et al.[26]	USA	Clinical trial	81 depressed patients with CHD	paroxetine and nortriptyline in depressed patients with CHD	Nortriptyline treatment was associated with a significantly higher rate of serious adverse cardiac events compared with paroxetine
Jeon et al.[27]	Korea	Animal study	4 animal sample	Nortriptyline and QT prolongation	Nortriptyline affects the ventricular repolarization process
Bar et al. [28]	Germany	Clinical trial	52 depressed subjects	cardio-respiratory coupling after treatment with nortriptyline	decreases of non-linear measures of heart rate variability in the nortriptyline group

Table 1. Review of the studies on the effects of antidepressants on cardiovascular system (Continue)

Author	Country	Study	Participants	End point	Finding
Kiev et al.[29]	USA	Clinical trial	58 depressed patients	Cardiovascular effects of nortriptyline in depressed outpatients	Slowing of cardiac conduction and possibly of rate-corrected repolarization
Thayssen et al.[30]	Germany	Clinical trial	21 elderly depressed patients	Cardiovascular effect of imipramine and nortriptyline in the elderly	Neither imipramine nor nortriptyline induced changes in cardiac conduction time measurements or arrhythmias
Giardina et al.[31]	USA	Clinical trial	Non-depressed cardiac patients	Imipramine and nortriptyline on left ventricular function and blood pressure	Neither drug significantly changed mean ejection fraction or peak systolic pressure end-systolic volume ratio
Hamer et al.[32]	UK	Cohort study	14,784 without CAD	Antidepressant use and future CVD	The use of TCAs was associated with elevated risk of CVD The use of SSRIs was not associated with CVD Neither class of drug was associated with all-cause mortality risk
Robinson et al.[33]	UK	Clinical trial	Depressed outpatients	Cardiovascular effects of phenelzine and amitriptyline	Amitriptyline significantly increased heart rate, while phenelzine produced slowing
Waslick et al.[34]	USA	Clinical trial	22 subjects	Cardiovascular effects of desipramine in children and adults during exercise testing	DMI has only minor effects on the cardiovascular response to exercise, and these effects do not appear age-related
Ho et al.[35]	Canada	Retrospective cohort	48,876 on venlafaxine 41,238 on sertraline	Adverse cardiac events of venlafaxine	Low to moderate dose venlafaxine is not associated with an increased risk of adverse cardiac events
Xue et al.[36]	USA	cohort study	64,000 cases	Duloxetine and cardiovascular events	The incidence of cardiovascular events did not differ among duloxetine initiators relative to other antidepressant but was higher than those without depression
Wernicke et al.[37]	USA	Meta-analysis	8504 depressed subjects	Cardiovascular safety profile of duloxetine	Use of duloxetine does not appear to be associated with significant cardiovascular risks
Scheen[38]	Belgium	cohort study	10 742 overweight/obese subjects	Cardiovascular risk-benefit profile of sibutramine	Drug should not be prescribed for overweight/obese patients with a high cardiovascular risk profile
James et al.[39]	UK	cohort study	10,744 overweight or obese subjects	Cardiovascular risk-benefit profile of sibutramine	Long-term sibutramine treatment had an increased risk of nonfatal MI and nonfatal stroke but not of cardiovascular death
Harrison-Woolrych et al.[40]	New Zealand	cohort study	15 686 overweight or obese subjects	Cardiovascular risk-benefit profile of sibutramine	Risk of death from a cardiovascular event in this general population of patients prescribed sibutramine was lower than has been reported in other overweight/obese populations
Maggioni et al.[41]	Italy	Cohort study	10,742 cases with CAD	Cardiovascular risk-benefit profile of sibutramine	overall mortality rate was low and sibutramine was well tolerated
Gaciong and Placha[42]	Poland	Cohort study	2225 overweight and obese subjects	Cardiovascular risk-benefit profile of sibutramine	Treatment with sibutramine resulted in clinically significant weight loss during short-term therapy in obese adults
Service and Waring[43]	UK	Case study	A depressed woman	QT prolongation and delayed atrioventricular conduction by ingestion of trazodone	The possibility of cardiotoxic effects after trazodone overdose
Krahn et al.[44]	USA	Retrospective	100 patients who received ECT	Cardiovascular complications in patients taking trazodone	Administering low-dose trazodone for insomnia in conjunction with ECT does not appear to increase cardiovascular complications
Boschmans et al.[45]	South Africa	Animal study	Heart rats	Coronary vascular responses after trazodone	Trazodone elicited a marked elevation in coronary flow over the dose range of 2.5-250 µM
Tulen et al.[46]	Netherlands	Clinical trial	10 depressed ones	Cardiovascular variability due to mirtazapine	Increase in heart rate and decrease in heart rate variability

SSRIs: Selective serotonin re-uptake inhibitors; ECG: Electrocardiogram; CAD: Coronary artery disease; ACS: Acute coronary syndrome; MI: Myocardial infarction; CHD: Coronary heart disease; AEs: Adverse events; TCAs: Tricyclic antidepressants; CVD: Cardiovascular disease; ECT: Electroconvulsive therapy; DMI: Desipramine

Results

First antidepressants group (SSRIs)

Most studies on cardiovascular effects of different types of SSRIs have emphasized neutralized or even beneficial cardioprotective effects of SSRIs especially newer generations on cardiovascular system. In a clinical trial study by Thase et al.[11] on 3298 depressed patients, escitalopram was used at doses between 5 and 20 mg/day for two acute (8-12 weeks) and long-term (24 weeks) phases to assess cardiovascular outcome including heart rate, blood pressure (BP), treatment-emergent AEs, and electrocardiograms (ECGs). The study showed no significant difference in BP, ECG, or cardiovascular AEs, but a slight decrease in heart rate without clinical consequences. In a similar study by Hanash et al.,[12] 240 patients were randomized to escitalopram 10 mg daily or matching placebo for 1-year and finally biochemical markers, as well as ECG and echocardiography patterns were assessed between study intervention groups. They could show similar findings between intervention and placebo groups in the incidence of ventricular arrhythmia and episodes of ST-segment depression, length of QTc, and systolic and diastolic echocardiographic measures as well as 1-year AEs including death, recurrent acute coronary syndrome, or need to repeating revascularization. Regarding the effects of sertraline and citalopram as other new types of SSRIs, Santangelo et al.,[13] 110 patients were treated with citalopram, 20-40 mg/day, or sertraline 50-100 mg/day leading considerable reduction in cardiovascular events in a 1-year follow-up time demonstrating cardioprotective effects of these two types of antidepressants on cardiovascular system in depressed patients. Glassman et al.[14] also assessed the effects of sertraline in patients with acute MI or unstable angina. In their study, depressed patients were randomly assigned to receive sertraline in flexible dosages of 50-200 mg/d or placebo for a treatment period of 6 months indicating no inter-group differences in the left ventricular function, ventricular arrhythmias, ECG patterns, and cardiovascular major AEs. The cardiovascular effects of sertraline have been also studies in children and young adolescents. In a study by Wilens et al.[15] on 107 children and 80 adolescents who suffered obsessive-compulsive disorder, cardiovascular effects of sertraline with the doses of < or = 200 mg/day for 12 weeks were assessed showing no clinically significant cardiovascular AEs in any of the subjects enrolled in the study assessed by ECG pattern and hemodynamic indices. Only, in a study by Weeke et al.,[16] increased risk for cardiac arrest was reported by administrating citalopram so that in a case-control study including 19,110 patients with the history of out-of-hospital cardiac arrest, the risk for cardiac arrest increased following use of citalopram with an odds ratio 1.29. The effects of first generations of SSRIs were assessed in the earlier studies. In a study Roose et al.[17] in 1998, 27 depressed patients were participated in an open medication trial of fluoxetine, up to 60 mg/day, for 7 weeks. The authors revealed a slight reduce in heart rate, a slight increase in systolic BP, and a slight increase in ejection fraction with no effect on cardiac conduction, ventricular arrhythmia, or orthostatic BP that all changes were reported to be tolerable. In another study by Yeragani et al.,[18] the administration of paroxetine was suggested to be cardio-protective especially with regard to sleeping, and awake heart period variability measures. In this regard, no adverse cardiovascular events was also reported by other authors such as Acharya et al.,[19] Pequignot et al.,[20] Zuidersma et al.,[21] Jerrell and McIntyre,[22] Grace et al.,[23] Swenson et al.,[24] and Taylor et al.[25] (Table 1) following the use of SSRIs.

Second antidepressants group (TCAs)

The cardiovascular effects of TCAs group of drugs have been into categories of their effects on left ventricular function and also on cardiac conduction system and ECG pattern. In a clinical trial by Roose et al.,[26] the use of nortriptyline with the dose of 50-150 ng/ml for 6 weeks led to a sustained increase in heart rate and also a reduction in heart rate variability. In an animal study by Jeon et al.,[27] the use of nortriptyline resulted in change of ventricular repolarization process indicated by the increase in QTc indicating the effect of nortriptyline on QT prolongation. In a study by Bar et al.,[28] 26 depressed subjects were treated with nortriptyline leading a decrease of non-linear measures of heart rate variability in addition to reduced cardio-respiratory coupling in the patients. In an earlier clinical trial study by Kiev et al.,[29] a treatment regimen including nortriptyline 75-150 mg/day led to adverse consequences such as a slowing of cardiac conduction. Contrarily, Thayssen et al.[30] in a clinical trial including elderly depressed patients who treated with imipramine or nortriptyline could not show significant changes in cardiac conduction time measurements or arrhythmias. With regard to the effects of TCAs on left ventricular functional status, Giardina et al.[31] conducted a clinical trial study on 20 non-depressed cardiac patients treated for ventricular premature depolarization. The patients

were administered 1 mg/kg/day imipramine or 0.5 mg/kg/day nortriptyline and finally showed that neither drug significantly changed mean left ventricular ejection fraction or peak systolic pressure end-systolic volume indicating the safety of those two drugs even in patients with impaired systolic function. Hamer et al.[32] in a cohort study could show no significant association between TCAs use and CHD events or all-cause mortality risk.

Regarding cardiovascular changes following the use of amitriptyline, amitriptyline usage is associated with significant prolongation of QRS and QTc as well as increased in heart rate while little overall change can be revealed in BP.[33] Furthermore, desipramine may be led to release serum norepinephrine may results in increase the risk of exercise-associated arrhythmias.[34]

Third antidepressants group (SNRIs)

With respect to the effects of SNRIs group on cardiovascular system, a limited number of studies have been conducted. In a recent retrospective study by Ho et al.[35] by reviewing the records of 48,876 an elder patients, who receiving venlafaxine, not only low to moderate doses of this drug had no adverse cardiovascular events, but also the lower risk of heart failure in comparison with other drugs such as sertraline was also shown. Regarding the effects of another type of drug in this group, duloxetine, Xue et al.[36] prospectively assessed the cardiovascular events in 17,386 depressed patients receiving duloxetine and showed no difference in the rate of AEs between depressed patients treated with duloxetine and untreated ones emphasizing occurrence of cardiovascular events by depression itself, not by duloxetine. In a meta-analysis by Wernicke et al.,[37] 42 placebo-controlled clinical trials of 8504 patients who were treated with duloxetine were systematically reviewed. They showed slight bit not significant decreases from baseline in RR, QRS, and QT intervals, as well as no increased risk of sustained BP elevation with duloxetine treatment. More attentions have focused the cardiovascular consequences of using sibutramine as a drug in the SNRIs group. In a study by Scheen,[38] the efficacy/safety ratio of sibutramine in overweight/obese high-risk subjects was prospectively assessed. In this cohort study, sibutramine 10 mg/day was administered for 6 weeks. Long-term follow-up of patients showed the increased risk for nonfatal MI and nonfatal stroke and thus it should not be recommended in obese subjects with previous history of cardiovascular disorders. In another cohort study by James et al.,[39] 10,744 overweight or obese older subjects, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both that received sibutramine were followed and similarly showed higher risk for nonfatal MI and nonfatal stroke in these patients. In another cohort study by Harrison-Woolrych et al.,[40] the studied cohort experienced significant AEs of hypertension, palpitations, hypotensive events and tachycardia, but with a low risk for cardiac death. Maggioni et al.[41] also indicated that only 3.1% of patients treated with sibutramine discontinued their regimen because of some slight complications including drug intolerance, headache, insomnia, nausea, dry mouth, and constipation-, tachycardia-, and hypertension and thus the drug was well tolerated. Gaciong and Placha[42] also showed that the patients received sibutramine in single daily doses of 10 and/or 15 mg experienced a tolerable decrease in systolic and diastolic BP and heart rate about 12 weeks of drug use.

Forth antidepressants group (SARIs)

In this group, trazodone has been more studied regarding its effects on cardiovascular system. According to the case-control study by Weeke et al.,[16] there was no association between the use of SARIs drugs such as trazodone and cardiac-related death. In a case study by Service and Waring[43] that described a woman who overdosed by acute ingestion of trazodone, significant QT prolongation and delayed atrioventricular nodal conduction was developed after injecting trazodone. In a retrospective study by Krahn et al.,[44] 100 patients who received electroconvulsive therapy with concurrent trazodone, except for orthostatic hypotension that was more observed in patients taking trazodone, no difference was revealed between these patients and the controls and thus using low-dose trazodone does not appear to increase cardiovascular AEs. In an animal study by Boschmans et al.[45] on hearts of the rats, trazodone could elicit a significant elevation in coronary flow over the dose range of 2.5-250 μM.

Fifth antidepressants group (NaSSAs)

Most studies performed on the cardiovascular effects of NaSSAs have mainly focused their effects on heart rate variability. However, the studies have reached contradictory results. In a meta-analysis study by Kemp et al.,[47] mirtazapine had no significant impact on heart rate variability. In a case study by Rajpurohit et al.[48] in 2014, subsequent to

the first dose of mirtazapine the patient experienced bradycardia and prolonged QRS as well as QTc intervals on ECG pattern. In a study by Terhardt et al.,[49] 21 moderately depressed patients being treated with mirtazapine that finally experienced increased heart rate and reduced heart rate variability compared with the non-depressed controls. In another trial study by Tulen et al.,[46] it was shown that although using mirtazapine had no effect on BP or BP variability, but early after use of this drug, increase in heart rate and decrease in heart rate variability could be observed might be due to the anticholinergic properties of this drug.

Discussion

According to the current review, we recommend to divide antidepressants into three categories based on the severity of cardiovascular adverse consequences including (1) the safest drugs including those drugs with cardio-protective effects on ventricular function as well as cardiac conductive system (SSRIs), (2) neutralized drugs with no evidenced effects on cardiovascular system (SNRIs), and (3) harmful drugs with adverse effects on cardiac function, hemodynamic stability, and heart rate variability (TCAs, SARIs, and NaSSAs). In fact, the cardiovascular effects of the variety of these drugs can referred to the chemical nature of the drug and its effect mechanism. Regarding the harmful cardiovascular effects of TCAs, it has been well demonstrated that blocking the reuptake of norepinephrine and serotonin at nerve terminals is responsible for their effects on cardiac arrhythmias and thus appearing heart conduction impairment. On the other hand, following sodium channel blockade induced by TCAs, prolonged intraventricular conduction in expected. In overdose of TCAs, this conductive prolongation may be also life-threatening because of tending increase in premature ventricular contractions and ventricular tachycardia.[31,50-53] Furthermore, the overdose of this drugs can result in suppressing potassium channels in myocytes leading QT interval prolongation and also appearing the pattern of torsades de pointes.[54,55]

In respect to the harmful effects of SARIs such as trazodone, although this group of drugs is structurally different from the TCAs, but because these drugs can selectively blocks the reuptake of serotonin describing their effects on decreasing BP. Furthermore, in some cases, the risk for premature ventricular contractions (PVCs) may be increased following the use of trazodone, however this group is suggested to be very safer than TCAs and thus can be a proper alternative for TCAs.[56,57] Along with safety of SARIs, the use of NaSSAs is not recommended in those with cardiovascular abnormalities because of their potential harmful effects on heart rate variability.

Different mechanisms have been identified regarding effects of SSRIs on cardiovascular system. These types of drugs can inhibit the reuptake of serotonin at presynaptic terminals, resulting in increased serotonergic activity in the interneuron space. In this regards, some protective effects of SSRIs may be related to their effects on vasculature, conduction system. One of the main beneficial effects of SSRIs in depressed patients is their effects on platelet activities. It has been shown that the depressed patients have elevated level of platelet adhesion and aggregation leading increased risk for cardiovascular events.[56,57] In fact, the use of SSRIs may prevent developing atherosclerotic plaques and also arterial thrombosis.[58-60] Along with their related beneficial effects, the harmful effects of SSRIs on cardiovascular system were only reported in less than 0.0003%[61] that can be only observed in drugs overdoses.

Conclusion

In conclusion, it seems that considering the new presented categorization of antidepressants can be clinically helpful to have the best selection for antidepressants to minimizing their cardiovascular harmful effects. However, the completeness of this categorization should be more assessed in further studies.

Acknowledgments

None.

Conflict of Interests

Authors have no conflict of interests.

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