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## Serotonin reuptake inhibitor antidepressants (SSRIs) against atherosclerosis

Greta Wozniak<sup>1</sup>, Aikaterini Toska<sup>2</sup>, Maria Saridi<sup>2</sup>, Odysseas Mouzas<sup>3</sup>

<sup>1</sup> Medical School, University of Thessaly, Larissa, Greece

<sup>2</sup> General Hospital of Korinthos, Korinthos, Greece

<sup>3</sup> Psychiatric Department, University of Thessaly, Larissa, Greece

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### Summary

Selective serotonin reuptake inhibitors (SSRIs) are a class of drug widely used for treatment of mood disorders, including depression and cardiovascular disease. A search for related articles in the PubMed database was attempted. It covered studies, reports, reviews and editorials of the last 5 years.

Pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 and IL-6, stimulate central serotonin (5-HT) neurotransmission and are over-expressed in depression, which has been linked with hypothalamic-pituitary-adrenal axis (HPA) hyperactivity. They have also been implicated in the pathogenesis and progression of other stress-induced disorders, like myocardial infarction (MI) and coronary heart disease (CHD), as they seem to modulate cardiovascular function by a variety of mechanisms. Biological mechanisms like these may explain the link between depression and CHD. There are a variety of environmental factors as well as genetic factors that might influence the pharmacogenetics of antidepressant drugs. New generation selective serotonin reuptake inhibitor antidepressants (SSRIs) causing a reduced cardiovascular morbidity and mortality may be related to serotonin platelet abnormalities in depressed patients that are effectively treated by SSRIs. SSRIs such as fluoxetine, paroxetine, sertraline and citalopram are not only considered to be free from the cardiotoxicity of their predecessors but also to function as safe and efficacious agents against depression, platelet activation, atherosclerosis and development and prognosis of coronary heart disease. However, there is a need for more studies in order to establish the exact biochemical mechanisms that are responsible for these diseases and the immunoregulatory effects of chronic use of SSRI medications.

**key words:** SSRIs • depression • cardiovascular disease • atherosclerosis • TNF- $\alpha$  • immune system

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**Author's address:** Greta Wozniak, Medical School, University of Thessaly, 41 110 Mezourlo, Larissa, Greece, e-mail: greta@med.uth.gr

## BACKGROUND

Depression and cardiovascular disease (CDV) are 2 of the world's leading health problems [1,2]. Depression has been linked with alterations in the immune system, the hypothalamic-pituitary-adrenal axis (HPA) in particular, which augments sympathetic activity via central regulatory pathways [3], as well as the elevated risk of developing coronary artery disease (CAD) [4]. Central and peripheral serotogenic transmission may be a common link between the 2 diseases [5]. SSRIs are widely used agents for treatment of mood disorders including depression [6], and they appear to be effective for treatment of depression in patients with ischemic heart disease (IHD) [7]. Moreover, they are thought to be much less cardiotoxic than other antidepressants and thus safer for patients with coronary heart disease (CHD) [8] than are tricyclics (TCAs). Although SSRI antidepressants reduce depression effectively, their use in cardiovascular disease remains controversial.

The purpose of this review was to gather information as to whether chronic use of SSRI antidepressants is protective against the atheromatic procedure by demonstrating biochemical mechanisms that may affect the function of the immune system and its response to inflammatory markers.

A search for recent articles related to depression, cardiovascular disease, the link between these 2 pathologic expressions and alterations in the immune system, such as expression of pro-inflammatory cytokines like TNF-alpha, IL-1 and IL-6 that occur in either of the two conditions, was attempted. The related articles were searched for in the PubMed database and covered studies, reports, reviews and editorials of the last 5 years. Older references served as auxiliary sources for comparison purposes.

## DEPRESSION AND ALTERATIONS IN THE IMMUNE SYSTEM

Various psychiatric disorders such as major depression [9], bipolar disorder [10], dysthymia [11] and schizophrenia [12] have been linked with alterations in the immune system [1].

In contrast to innate immunity, the adaptive immune system is antigen-specific and operates through T and B cells [13,14]. In innate immunity cytokines are produced by macrophages and natural killer cells, while in adaptive immunity they are produced by the T-lymphocytes [15,16]. More specifically, IL-1, IL-6 and TNF act as pro-inflammatory cytokines stimulating immune cells' anti-inflammatory cytokines IL-4 IL-10 and IL-13, which hinder the production of other cytokines. Cytokines produced by the innate response the type of adaptive response. These are large polypeptide mediators (8–60 kDa) that regulate growth, differentiation and function of many cell types. Most commonly cytokines have been classified into families of interleukins, TNFs, interferons (INFs), chemokines, haematopoietins and colony-stimulating factors (CSFs). As many cytokines exert a number of different actions, they may in fact belong to more than one cytokine family [14].

Moreover, pro-inflammatory cytokines stimulate central serotonin (5-HT) neurotransmission. IFN- $\alpha$  stimulates the enzyme indoleamine 2, 3-dioxygenase (IDO) that reduces the production of 5-HT in the brain [17]. A polymorphism of

the IL-6 gene is associated with reduced risk of depression with interferon therapy [14], although Hong et al suggested that the investigated IL-6 polymorphism does not affect major depressive disorder (MDD) susceptibility [18]. However, it has not been clearly stated whether or not pro-inflammatory cytokines interact with IDO, resulting in functional mood disorder [19].

Pro-inflammatory cytokines are endogenously over-expressed in depression and other stress-induced disorders [20]. Depression has been linked with hypothalamic-pituitary-adrenal axis (HPA) hyperactivity [17]. Depressed patients show elevated corticotrophin releasing factor (CRF) in cerebrospinal fluid (CSF), blunting of ACTH response to CRF, hypercortisolemia, and pituitary and adrenal gland enlargement [5,14]. Furthermore, major depression is associated with a pro-inflammatory response, as there is an elevation in C-reactive protein and in cytokines such as IL-6 and TNF- $\alpha$  [14].

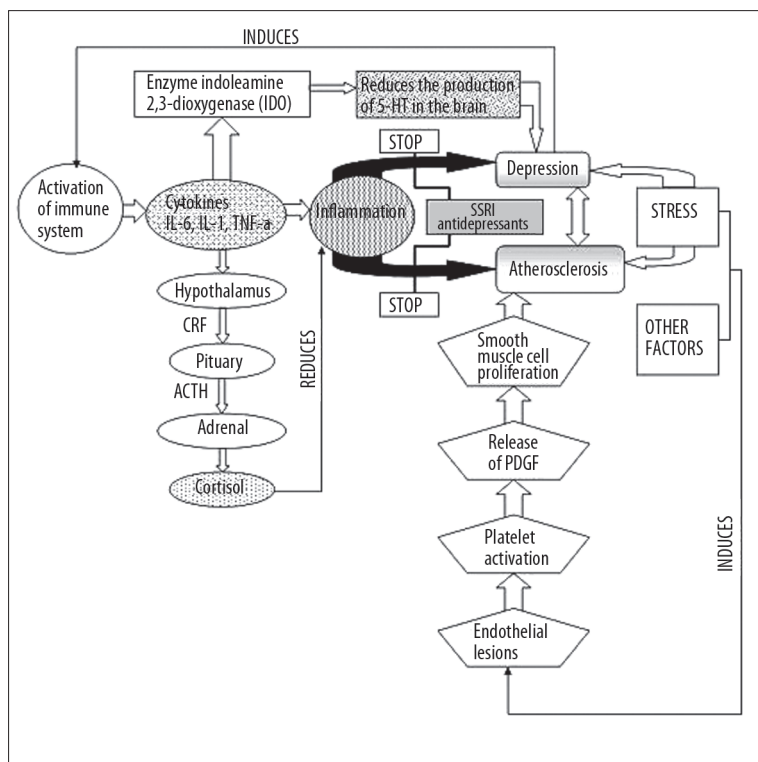
Torpey et al came to the conclusion that although antidepressant medications and some forms of psychotherapy are efficacious in treating chronic depression, their combination appears to be superior to either monotherapy alone, and that chronic depression is often inadequately treated [21].

## INFLAMMATORY MARKERS AND ATHEROSCLEROSIS PROGRESSION – LINK BETWEEN DEPRESSION AND CORONARY HEART DISEASE

Atherosclerosis is a long-term process. Cholesterol and other substances are accumulated in the form of deposits that at some point clog blood vessels, thus causing myocardial infarction (MI), commonly known as "heart attack". Both heart attacks and angina are expressions of what is known as coronary heart disease (CHD), the etiology and prognosis of which have been much studied recent years. Psychosocial factors such as depressive and anxiety disorders, temperament factors and chronic life stressors have been thought to have a direct relationship with the development and prognosis of CHD [22].

Whooley et al. studied a sample of outpatients with coronary heart disease and came to the conclusion that the association between depression and adverse cardiovascular events was explained by behavioural factors, particularly physical inactivity [23].

Pro-inflammatory cytokines such as TNF, IL-1 and IL-6 have been implicated in the pathogenesis and progression of heart failure (HF) as they seem to increase in such patients [3]. The pro-inflammatory cytokine TNF- $\alpha$  seems to modulate cardiovascular function by a variety of mechanisms. Berthonneche et al. showed that it is expressed in the heart and contributes to myocardial dysfunction and ventricular dilation 7 days after MI in rats, thus leading to the development of chronic heart failure (CHF) [24]. Moreover, Toufekistan et al. tried to determine whether anti-TNF- $\alpha$  treatments could be used as therapeutic interventions for improvement of MI outcome. Thus, they used a single intravenous injection of soluble TNF- $\alpha$  receptor at the time of reperfusion and they tried to find whether it could reduce the infarct size and improve post-ischemic cardiac function *in vivo* in rats. They concluded that inhibition of increased



**Figure 1.** Depiction of immune system activation in depression and atherosclerosis. Pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 and IL-6, stimulate central Serotonin (5-HT) neurotransmission through IFN- $\gamma$  activation of the enzyme indoleamine 2, 3-dioxygenase (IDO) that reduces the production of 5-HT in the brain. These cytokines are over-expressed in depression, which has been linked with hypothalamic-pituitary-adrenal axis (HPA) hyperactivity. Thus, increased production of pro-inflammatory cytokines, play the role of an important mediator of inflammation. On the other hand, the pro-inflammatory protein TNF-alpha is known to be involved in inflammatory endothelial injury and atherosclerotic changes. Stress does not only induce depression, but along with environmental factors, such as nutrition, smoking, exercise and prescribed drugs, as well as genetic factors, also induces the inflammatory cascade that leads to the development of atherosclerosis through activating endothelial lesions, which in turn activate platelets and through release of platelet-derived growth factor (PDGF) which plays a role in cell proliferation, atherosclerosis begins. The cardiovascular function is also modulated by pro-inflammatory cytokines, which have been implicated in the pathogenesis and progression of stress-induced disorders. Thus, inhibition of inflammation by use of SSRI antidepressants might actually be beneficial.

TNF- $\alpha$  production by a single IV injection of sTNFR-Fc improved post-infract outcome in rats [25].

The literature is unclear as to whether inflammation observed in depressed patients is a trait-marker of depression or whether inflammation contributes to the pathogenesis of depression [3]. Activation of pro-inflammatory cytokines allows the myocardium to respond to tissue injury and maintain homeostasis through the promotion of tissue repair (Figure 1). This inflammatory cascade plays an adaptive role early in the development of heart failure. On the other hand, it has been suggested that interleukins and other cytokines might cause depression [3].

Kim et al. showed that pre-treatment of mesenchymal stem cells (MSC) prior to transplantation with TNF- $\alpha$  increases adhesiveness. TNF- $\alpha$  is released from ischemic heart after acute MI, increases the production of other cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and it seems to activate nuclear factor kappa B (NF-kappa B), thus up-regulating the expression of molecules involved in inflammation and cell adhesion [26].

Kempf et al. also suggested that while IL-6 was significantly increased in serum from acute myocardial infarction (AMI) patients, IL-6 mRNA levels did not differ between patients and controls, while TNF- $\alpha$  mRNA expression rates and concentrations in serum were significantly elevated in AMI patients [27].

It has been proposed that depression exerts an adverse impact on the cardiovascular system. Increased heart rate, blood pressure, cardiac arrhythmias, platelet aggregation and inflammation are some of the negative expressions of depression on the cardiovascular system. There is a 2-fold

risk of morbidity and mortality of CHD for patients with depression; therefore, management of depression may contribute to modification of the development and prognosis of CHD [22]. Whang et al. found that symptoms of depression are indeed associated with higher risks of cardiac events, although they concluded that use of antidepressants might be a marker of worse depression, and thus there is a need for further study [28].

Contrary to the adverse cardiac effects of the tricyclic group of antidepressants, the SSRI group seems to be safe and efficacious in depressed CHD patients [29], as it can reduce cardiac morbidity and mortality [30]. Goldston et al. have reviewed the biological mechanisms that may explain the link between depression and CHD and concluded that cardiologists may be reluctant to add an antidepressant to the treatment of cardiac patients [22].

#### EFFECTS OF SSRIs ON THE DEVELOPMENT AND PROGNOSIS OF ATHEROSCLEROSIS

Binder et al. proposed in their review that a variety of environmental factors such as nutrition and other prescribed drugs as well as genetic factors might influence the pharmacogenetics of antidepressant drugs. It seems that polymorphisms

in genes that regulate the hypothalamus-pituitary-adrenal (HPA) axis affect response to antidepressants [31].

Malarstig et al. suggested that there is no association of TNFSF4 variation with incident CVD in women, but there appears to be one with incident venous thromboembolism [32]. However, Olofsson et al. demonstrated that the immune co-stimulatory factor TNFSF4 is expressed in human atherosclerotic lesions [33]. Manginas et al. also suggested that polymorphisms of the TNF- $\alpha$ , INF- $\gamma$  and IL-10 groups do not contribute to the development of stable angina (SA), unstable angina (UA), or myocardial infarction (MI), with the exception of a possible link of IL-6-174 G/C polymorphism with the susceptibility of developing MI [34].

The most commonly prescribed class of antidepressants nowadays are the selective serotonin reuptake inhibitors (SSRIs), which include sertraline, fluoxetine, citalopram, bupropion and mirtazapine, all of which appear to be safe to use after MI [35]. The cardiovascular effects of SSRIs that have been studied during the last 5 years are shown in Table 1.

SSRI antidepressants inhibit serotonin's reuptake into the presynaptic cell, thus increasing its extracellular level. They are usually prescribed for depression [36], social anxiety, panic disorders [37], obsessive-compulsive disorder [38] and sometimes for posttraumatic stress disorder [2,39].

Hattori et al. attempt to explain the effect of SSRI drugs biochemically, stating that there is an underlying decrease in the function of brain monoaminergic neurotransmitters activated, such as by serotonin and noradrenalin [40].

Kubera et al. tried to determine whether 5-HT and 5-HT receptor subtypes affect IL-6 and TNF- $\alpha$  production. In inflammatory conditions 5-HT is released after stimulation by endotoxic lipopolysaccharide, platelet activating factors and IFN- $\gamma$ . 5-HT inhibits the production of TNF- $\alpha$  and promotes the production of IFN- $\gamma$ . The study concluded that intracellular 5-HT is necessary for cytokine production by immune cells and that the production of IL-6 and TNF- $\alpha$  is suppressed by elimination of endogenous serotonin [41].

Narita et al. suggested that a mechanism that possibly explains the prevention of atherosclerosis within the immune system context is based on adiponectin, which is an adipose tissue-specific plasma protein. Adiponectin is involved in insulin sensitization and has anti-atherosclerotic properties. On the other hand, the pro-inflammatory protein TNF-alpha is known to be involved in inflammatory endothelial injury and atherosclerotic changes. Since antidepressant medications seem to decrease the production of pro-inflammatory cytokines, including TNF-alpha, Narita et al. examined the plasma levels of TNF-alpha and adiponectin in patients with remitted depressions, which were under maintenance antidepressant treatment for longer than half a year. The remitted depression group had significantly lower levels of TNF-alpha and higher levels of adiponectin than those in the control group. Thus, it is possible that maintenance antidepressant therapy may have anti-inflammatory effects and prevent the development of atherosclerosis [42].

Whooley et al. found that there is no association between plasma inflammatory mediators and depression in their

cross-sectional study of 984 CAD patients, which could be explained by the effects of the prescribed medications that included statins, b-blockers and antidepressants [43,44]. Lanza et al. also showed that patients who failed to respond to SSRIs appeared to have higher inflammatory mediator levels than healthy controls and euthymic patients who had failed SSRI treatment [45].

Kim et al. found higher baseline concentrations of IL-6 and TNF- $\alpha$  in depressed SSRI-resistant patients when compared with healthy controls [46]. O'Brien et al. agree that patients resistant to SSRIs showed higher production of TNF- $\alpha$  [47]. According to Himmerich et al, soluble TNF receptors increased significantly in plasma concentration after antidepressant treatment, but TNF- $\alpha$  concentration did not show significant increase [48].

According to Diamond et al. antidepressant treatment had significant effects on lipopolysaccharide-stimulated production of proinflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$  and IL-12. They found that antidepressants suppress IFN- $\gamma$  production [49]. Moreover, it is stated elsewhere that SSRI use in chronic posttraumatic stress disorder seems to decrease the levels of baseline diurnal cortisol and cortisol reactivity to stress [2]. According to Cohen et al. there is a significant autonomic dysregulation at rest that in posttraumatic stress disorder patients, which is corrected by treatment with SSRIs [39]. Narita et al. reported that there was a significantly lower TNF- $\alpha$  level in remitted patients suffering from depression who were receiving antidepressant treatment for longer than 6 months, compared to healthy subjects [50].

Tsao et al. suggested that pro-inflammatory cytokines and 5-HTT might play critical roles in the pathogenesis of major depression. Furthermore, cytokine levels were affected by chronic treatment with 5-HTT inhibitors and mRNA expressions of IL-1 $\beta$ , IL-6, IFN $\gamma$  and TNF $\alpha$  were higher in the depressed patients than in healthy controls [51].

It has been suggested that treatment of depression with SSRIs may reduce major heart disease events [52]. Although some studies have found a reduced relative risk for MI in patients using SSRIs, use of SSRIs in depressed patients who experience an acute MI may reduce subsequent cardiovascular morbidity and mortality. Use of SSRIs was associated with 43% lower risk of death or nonfatal MI and 43% lower risk of all-cause mortality [30]. According to Gehi et al. non-compliance to medication for major depression in patients with stable coronary disease may adversely affect cardiovascular outcomes [53]. Cohen et al. found that use of any antidepressant medication was associated with MI, cardiovascular hospitalization and all-cause mortality, but incidence of MI was lower for patients using SSRIs compared to tricyclic agents, as it is possible that SSRI treatment might ameliorate the adverse effect of depression on cardiovascular disease [54]. Barton et al. investigated the possibility that treatment with SSRI medication would modify sympathetic activity in a way that cardiac risk might be reduced. Data obtained from 39 patients revealed that following treatment with an SSRI, both sympathetic and sympathoadrenal activity were markedly reduced, but it is difficult to ascertain whether this effect is specific or non-specific [55]. On the other hand, Bär et al. suggested that antidepressant treatment leads to significant change of the parasympathetic



**Table 1.** Depiction of usually utilized SSRIs and their cardiovascular effects as studied in the last five years.

SSRI medications	Recent studies mentioning the cardiovascular role of SSRI medications	Effects of SSRIs
Citalopram	Taylor D (2008)	<ul style="list-style-type: none"> <li>• May decrease the risk of MI</li> <li>• May improve mortality following stroke</li> <li>• Few cardiovascular adverse effects</li> </ul>
	Muldoon MF, Mackey RH, Sutton-Tyrrell K, Flory JD, Pollock BG, Manuck SB (2007)	<ul style="list-style-type: none"> <li>• Individual differences in central serotonergic responsivity are inversely related to preclinical vascular disease</li> </ul>
Paroxetine	Taylor D (2008)	<ul style="list-style-type: none"> <li>• May improve mortality following stroke</li> <li>• Few cardiovascular adverse effects</li> </ul>
	Roose SP, Miyazaki M (2005)	<ul style="list-style-type: none"> <li>• Normalized platelet activity at low doses</li> <li>• Were not associated with significant cardiac symptoms</li> </ul>
Escitalopram	Angermann CE, Gelbrich G, Störk S, Fallgatter A, Deckert J, Faller H, Ertl G (2007)	<ul style="list-style-type: none"> <li>• Attempted to assess the effects of antidepressant pharmacotherapy and their safety in CHF patients</li> </ul>
	Eller T, Vasar V, Shlik J, Maron E (2008)	<ul style="list-style-type: none"> <li>• Responders to treatment have lower TNF-<math>\alpha</math> baseline</li> <li>• Lower release or synthesis of TNF-<math>\alpha</math> may contribute to a better efficacy of escitalopram in depressed patients</li> <li>• The antidepressants could influence cytokine levels independently of their therapeutic effects</li> </ul>
Sertraline	Roose SP, Miyazaki M (2005)	<ul style="list-style-type: none"> <li>• Were not associated with significant cardiac symptoms</li> </ul>
	Serebruany VL, Suckow RF, Cooper TB, O'Connor CM, Malinin AI, Krishnan KRR, van Zyl LT, Lekht V, Glassman AH (2005)	<ul style="list-style-type: none"> <li>• Sertraline treatment suppressed platelet function</li> </ul>
	Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, Göka E (2005)	<ul style="list-style-type: none"> <li>• Positive influence of SSRI treatment on platelet reactivity of depressed patients</li> </ul>
Fluoxetine	Parissis J, Fountoulaki K, Paraskevaidis I, Kremastinos DT (2007)	<ul style="list-style-type: none"> <li>• Relief from their depressive symptoms</li> <li>• Improvement in quality of life</li> <li>• Potential benefit in their cardiovascular risk</li> </ul>
	Roose SP, Miyazaki M (2005)	<ul style="list-style-type: none"> <li>• Were not associated with significant cardiac symptoms</li> </ul>
	Tsao CW, Lin YS, Chen CC, Bai CH, Wu SR (2006)	<ul style="list-style-type: none"> <li>• Administration of fluoxetine caused a marked decrease in IFN<math>\gamma</math> mRNA expression</li> <li>• There was no significance in IL-1<math>\beta</math> and TNF-<math>\alpha</math> as compared to the healthy controls</li> <li>• There was no difference in IL-6 between patients and controls</li> <li>• Levels of cytokines and 5-HTT might represent a modulatory mechanism between an immune response to the central nervous system and the pathogenesis of depression</li> </ul>

function, as SSRIs influence cardiac function, and that it is not possible to estimate the long-term consequences of these changes [56]. Wong et al. supported the notion that successful antidepressant treatment ameliorates hemorheological measures of stress-hemoconcentration, which contribute to an increased risk for CVD. This is accomplished by alleviating the advancement of atherosclerotic plaque in the arteries through improving the symptoms of major depressive disorder (MDD) [57].

Somberg et al. reviewed possible explanations for this increased morbidity in patients with a combination of depression with CAD, and concluded that SSRIs causing a reduced cardiovascular mortality may be related to serotonin

platelet abnormalities in depressed patients that are effectively treated by SSRIs. They also proposed that it is possible that the SADHART and ENRICH trials reveal a mechanism of depression that also affects platelet function and can be improved with SSRI treatment [52,58].

Delaney et al. suggested that there is a difference in utilization of antidepressants between different ethnic groups. In a US-based prospective cohort, Caucasian participants had the highest rate of antidepressant medication use (12%) compared with African-American (4%), Asian (2%) and Hispanic (6%) participants [59]. As for patients with CHD, Waldman et al. found that African-Americans are less likely to be treated with antidepressants compared with whites,

even though there is no difference in the severity of depressive symptoms, and African-Americans have a significantly greater risk of dying from CHD compared to whites [60].

### Adverse effects of SSRIs

Adverse effects associated with SSRIs are common during the first 3 months of treatment and they are bothersome to patients. Patients usually develop sexual dysfunction, drowsiness and blurred vision [36]. According to an earlier study by Kim et al. there was no increased risk for bleeding associated with SSRI use for patients who received antiplatelet and anticoagulant therapy for acute coronary syndromes [61].

Pacher et al. reviewed the cardiovascular adverse effects of antidepressants and found that mild bradycardia, insignificant prolongation of QT interval, dysrhythmia syncope and orthostatic hypotension were associated with consumption of a variety of SSRIs [62]. Moreover, it was mentioned that there is very little evidence of orthostatic hypotension during fluoxetine treatment, but in the overdosed patients fewer cardiac symptoms were reported than with tricyclic antidepressants [63].

Baumet et al. concluded that in patients suffering from depression or panic disorder, QT variability is not correlated with cardiac norepinephrine spillover and is not affected by treatment with SSRIs [64]. Isbister et al. showed that SSRIs are relatively safe in overdose despite serotonin syndrome being common, except for citalopram, which was significantly associated with QTc prolongation [65].

According to Licht et al. certain antidepressants is associated with both high diastolic and systolic blood pressures and hypertension [66].

### Citalopram and paroxetine

Taking into consideration the association between depression and cardiovascular disease, it has been suggested by Taylor that the use of SSRI medication may decrease the risk of MI, that citalopram and paroxetine may improve mortality following stroke, and that SSRIs generally have few cardiovascular adverse effects [35].

Muldoon et al. tested the hypothesis that a blunted central serotonergic response would be associated with preclinical atherosclerosis. They administered citalopram as a pharmacological agent to 244 adults receiving no medications affecting cardiovascular or serotonergic function and found that prolactin response was associated with carotid artery thickening, thus concluding that individual differences in central serotonergic responsivity are inversely related to preclinical vascular disease [67].

Roose et al. agreed that treatment with paroxetine normalized platelet activity, an effect that occurred when the specific medication was administered at low doses, and that fluoxetine, paroxetine and sertraline were not associated with significant cardiac symptoms [7].

### Escitalopram

Angermann et al. recently conducted a MOOD-HF trial in attempting to assess the effects of antidepressant

pharmacotherapy on hard somatic endpoints, the mechanisms of action of SSRI treatment (particularly the use of escitalopram), and their safety in CHF patients [68]. Eller et al. on the other hand, investigated the acute and chronic effects of escitalopram in 100 patients with major depression who were treated with 10–20 mg daily. The comparison of baseline cytokine levels between responders, non-responders and healthy subjects showed a difference for TNF- $\alpha$ , with the responders having lower TNF- $\alpha$  baseline. This indicates that lower release or synthesis of TNF- $\alpha$  may contribute to a better efficacy of escitalopram in depressed patients. They also suggested that, due to the fact that it is not known whether immunological disturbances in depression are directly related to symptomatic status, the antidepressants could influence cytokine levels independently of their therapeutic effects [1].

### Sertraline

According to Goodnick et al, since cardiovascular complications can be related to platelet clumping, reductions in morbidity can be achieved by reducing platelet adhesiveness. Thus, sertraline administration appears to be safe in the post-myocardial infarction (MI) state [69].

Serebruany et al. demonstrated that sertraline treatment suppressed platelet function, as platelet/endothelial biomarkers were negatively correlated to the plasma levels of sertraline [6]. Basterzi et al. also agree with the positive influence of SSRI treatment on platelet reactivity of depressed patients [70]. Likewise, Serebruany et al. demonstrated in an earlier study [71] that sertraline and probably other SSRIs improve platelet markers even in the presence of aspirin. They have also shown in a more recent study [6] that plasma levels of sertraline and N-desmethylsertraline is negatively correlated with the release of platelet/endothelial markers, thus proving that use of sertraline in therapeutic concentrations exhibits antiplatelet and endothelium protective properties.

Parisis et al. also agree that sertraline intervention provides depressed patients not only with relief from their depressive symptoms and improvement in quality of life, but also a potential benefit in their cardiovascular risk [72].

### Fluoxetine

In an earlier review Pacher et al. suggested that fluoxetine may cause significantly fewer anticholinergic, antihistaminergic and cardiotoxic side-effects in the treatment of major depressive disorders. Chronic treatment with fluoxetine was not reported to affect the electrocardiogram (ECG) [63].

Moffit et al. concluded that short-term treatment with the SSRI fluoxetine in rats enhances baroreflex control of sympathetic nervous system activity [73]. Tsao et al. showed that administration of fluoxetine caused a marked decrease in IFN $\alpha$  mRNA expression, there was no significance in IL-1 $\beta$  and TNF- $\alpha$  as compared to the healthy controls, and there was no difference in IL-6. Thus, levels of cytokines and 5-HTT might represent a modulatory mechanism between an immune response to the central nervous system and the pathogenesis of depression [51].

Magyar et al. showed that fluoxetine exerts much stronger suppressive effect on cardiac than neuronal calcium channels [74].

## DISCUSSION

Clinical and experimental studies indicate that stress and depression are associated with the up-regulation of the immune system. Increased production of pro-inflammatory cytokines [75] such as TNF- $\alpha$  play the role of an important mediator of inflammation. Thus, inhibition of its activity might actually be beneficial [76]. Increase in the production of pro-inflammatory cytokines [41] and enhanced platelet activity in depression may increase mortality in coronary disease [77], thus suggesting that antidepressive treatments have negative immunoregulatory and antiplatelet effects [41]. *In vitro* culture and animal studies have shown that antidepressants decrease the production of pro-inflammatory cytokines. All depressive patients do not share immunological disturbances, including changes in cytokine levels. This leads to the conclusion that the immunomodulatory action of antidepressants plays a therapeutic role only in certain groups of patients [75].

Elsewhere it has been stated that pro-inflammatory cytokines like IL-6 and TNF- $\alpha$  can activate macrophages within atherosclerotic plaques, which indicates a process finally leading to plaque development and rupture [78]. This causes an increase in plasma pro-inflammatory cytokines to patients with UA. This is also supported by Huang et al, who showed that activation and overexpression of poly (ADP-ribose) polymerase-1 (PARP-1) in mononuclear cells were positively associated with increased plasma levels of TNF- $\alpha$  and IL-6 in patients with UA. Thus, inhibition of PARP-1 may be useful for the treatment of systemic inflammatory responses in these patients [79].

Since TNF- $\alpha$  and IL-6 have proven to be deleterious to atherosclerotic plaques by provoking plaque instability, finding ways to reduce them might decrease the risk of CHD [80].

O'Brien et al. suggested that future antidepressants may target the immune system by either blocking the actions of pro-inflammatory cytokines or increasing the production of anti-inflammatory cytokines [81]. The relationship between depression and CHD might refer to vascular inflammation, autonomic and endothelial dysfunction, and behavior patterns such as poor adherence to medication and advice [82].

Earlier [63] as well as recent [83–86] studies and reviews mention the possible general and cardiovascular effects of fluoxetine and other new SSRIs antidepressants found in animals, suggesting possible explanations of the lower incidence of cardiovascular events in humans following SSRI treatment. However, the largest randomized trial – ENRICHD – that tried to determine whether mortality and recurrent MI are reduced by treatment of depression using SSRIs showed that although the risk of death or nonfatal MI was significantly lower in patients taking SSRIs, the intervention did not increase event-free survival [87].

Hesslinger et al. discussed the differential therapeutic consequences of SSRIs, mentioning that depressive disorders are rarely diagnosed, and only a minority of patients receive adequate treatment, although the number of treatment options has increased in recent years [88]. The most commonly prescribed antidepressant agents are Sertraline (18%), Escitalopram (14%) and Amitriptyline (10%), and

the most commonly prescribed class of antidepressants are the SSRIs (55%). SSRIs became available in the late 1980s and seem to be the most popular and commercially successful antidepressants in the US [77].

It has been shown by a number of studies that SSRI use is associated with a lower risk of re-infarction and mortality. This is probably due to the effects of SSRIs on platelets. In an earlier study Musselman et al. treated depressed patients with paroxetine and demonstrated that platelets showed increased activation before and normalization after treatment [89]. The post-hoc secondary analyses from the ENRICHD study supports this notion [30].

Halperin et al. suggested that fluoxetine, paroxetine, and sertraline are drugs with the highest degree of serotonin reuptake inhibition and they are frequently associated with abnormal bleeding and modifications of hemostasis markers. Among the most frequent hemostatic abnormalities, decreased platelet aggregability and activity and prolongation of bleeding time are mentioned [37].

According to Blanchette et al, of the 7051 elderly patients included in their study, 5.4% indicated they became depressed within 6 months of having a thromboembolic episode (TEE). Of the total population of antidepressant users (68.2% of depressed elders), 76.4% used SSRIs. Neither antidepressant use nor SSRI use was associated with an increase or reduction in risk of using health care services, including hospitalizations and ED visits, in the 12 months following a TEE [90].

Glassman et al. explored the evidence that treating depression reduces the increased risk of cardiovascular morbidity and mortality. SSRI antidepressants seem to be safe and effective and they may reduce not only depression but medical adverse events as well. However, they conclude that this evidence is not definitive [91].

Thombs et al. agreed that depression treatment with medication or cognitive behavioral therapy resulted in modest reductions in depressive symptoms, but there was no evidence that depression treatment improved cardiac outcomes [92]. Swenson et al. also concluded that after reviewing antidepressant trials in high-risk patients, they did not determine whether SSRIs are associated with a greater or lesser risk of cardiovascular adverse events [93].

According to Goodnick et al. the rate of comorbid depression and medical illness varies from 10% to 40%. Citalopram, sertraline, paroxetine, fluoxetine and bupropion in post-stroke depression and sertraline in post-MI state seem to be safe and efficacious [69]. It has also been suggested that SSRIs, and especially fluoxetine, may be responsible for the inhibition of platelet aggregation, which in synergy with chronic sertraline administration may lead to low platelet activity [6].

Depression and cardiovascular disease are closely associated clinical entities, the former of which appears both to cause and worsen the latter [35,97,98]. Psychological stress has been identified as a contributor to the pathogenesis of atherosclerosis and hypertension and as a risk factor for CVD and coronary events [94,96]. Many antidepressants, such as tricyclic drugs, have many cardiotoxic properties, while others (such as the SSRIs) have neutral or beneficial effects in

various cardiovascular disorders [35]. Evidence shows that treatment of MDD patients who experience an acute MI with SSRI antidepressants might decrease mortality or cardiac events [95]. Of the 4 ethnicities, Caucasian had the highest rate of antidepressant medication (ADM) use compared with African-Americans, Asians and Hispanics [59]. The new generation of SSRIs, such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and venlafaxine, are not only considered to be free from the cardiotoxicity of their predecessors [62], but also to function as safe and efficacious agents against depression, platelet activation, atherosclerosis and development and prognosis of coronary heart disease. However, there is a need for more clinical studies in order to establish the exact biochemical mechanisms that are responsible for these diseases and the immunoregulatory effects of chronic use of SSRI medications.

## CONCLUSIONS

Antidepressants are safe and efficacious agents against depression, platelet activation, atherosclerosis, and development and prognosis of coronary heart disease.

Their use is associated with a lower risk of re-infarction and mortality and may be responsible for the inhibition of platelet aggregation, which may lead to low platelet activity.

## APPENDIX

The table consists of three columns, the first of which is a list of SSRI medications which have been studied in the last five years or otherwise mentioned by the authors in articles concerning human reactivity to such treatment, the second one referring to the names of the authors and the year of publication of their articles and the third one demonstrating the conclusions of these articles concerning the immunoregulatory and the cardiovascular role of SSRI medications.

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