

## Novel Antidepressant Drugs, Arterial Hypertension and Cardiovascular Disease

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**Abstract:** Depression is a common mental health issue worldwide leading to disability, functional decline and increased mortality. Novel antidepressants have been developed during the last decades in order to treat depression syndromes. Some evidence suggests that major depression has been associated with the development of congestive heart failure and with adverse outcomes in patients with coronary heart disease. The purpose of the present article is to review the impact of novel antidepressant patent drugs on cardiovascular disease and arterial hypertension.

**Keywords:** Arterial hypertension, bupropion, cardiovascular disease, depression, fluoxetine, norepinephrine reuptake inhibitors, serotonin reuptake inhibitors.

### INTRODUCTION

Depression is a common psychiatric condition characterized by affective, cognitive, and psychomotor symptoms that interfere with a person's ability to work, study, deal with interpersonal relationships, and enjoy once-pleasurable activities [1]. In the last years, the burden of the disorder has increased so that it is estimated by the World Health Organization that it will become the second cause of disability worldwide with a heavy economic burden for the western societies [2]. As a clinical entity, depression is commonly related to cardiovascular disease. Although the pathophysiology beyond that is not fully established, depression has been recognised as a risk factor for cardiovascular morbidity and mortality but at the same time is a co morbid condition in patients with various cardiovascular diseases [3, 4]. 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. For these reasons it is strongly recommended that all patients diagnosed with depression should be closely monitored for other factors (obesity, hypertension, diabetes, physical inactivity, lipid profile) associated with cardiovascular disease and advised to medical interventions that reduce cardiovascular risk.

Even though the available antidepressants have consistently improved the prognosis of the disorder, their results

are far from being satisfactory not only due to their limited effectiveness but their considerably side effects, with regard especially to oldest representatives [5]. One of the first antidepressant agents that were introduced in 1950s was imipramine [6]. Imipramine with the patent number US5658590 is a tricyclic antidepressant (TCA) and acts through the inhibition of the reuptake of the monoamines serotonin (5-HT) and norepinephrine (NE). TCAs also have affinity for  $\alpha_1$ ,  $H_1$ , and muscarinic receptors, thus causing anticholinergic adverse effects [4]. These drugs have not been prescribed very often. Since then a number of monoamine oxidase inhibitors and tricyclic antidepressants have been developed Fig. (1), considering as the first line of pharmacotherapy for the major depressive disorder [7].

Over the last few years, due to their common side effects that lead to discontinuation of treatment, the usual treatment with tricyclic antidepressants (TCA) has been replaced by the introduction of novel antidepressants Fig. (2). The most common cardiovascular effects of TCAs included orthostatic hypotension, which often resulted in haemodynamic instability, especially in patients with conduction system disease and congestive heart failure [8]. Furthermore, TCA's beyond their significant anti-arrhythmic activity (type IA anti-arrhythmic agents), also show arrhythmogenic potential [9] thus raising safety considerations especially in patients with cardiovascular disease.

Novel antidepressants include selective serotonin reuptake inhibitors (SSRIs; i.e. fluoxetine (patent number EP0123469B1 [10]), paroxetine (patent number WO2001012624 [11]), citalopram (patent number WO2002053133A1 [12]), escitalopram (patent number

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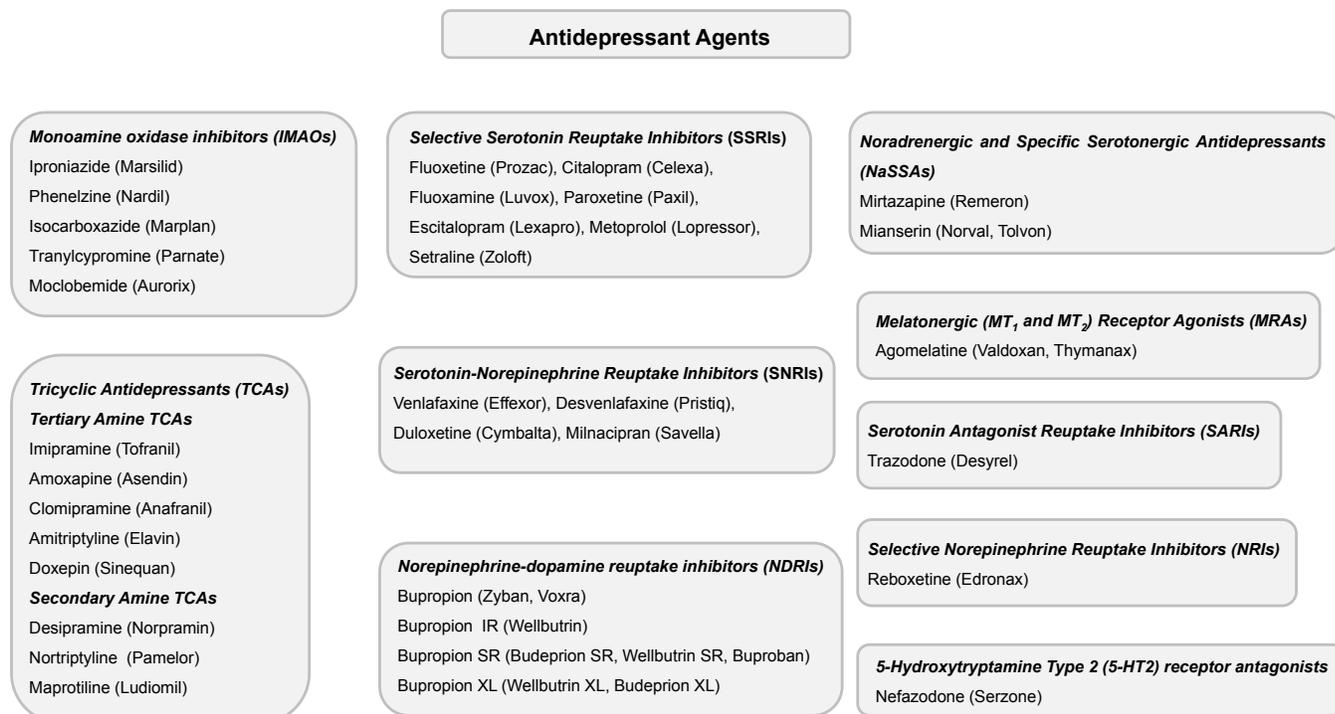


Fig. (1). Classes of clinically antidepressant drugs.

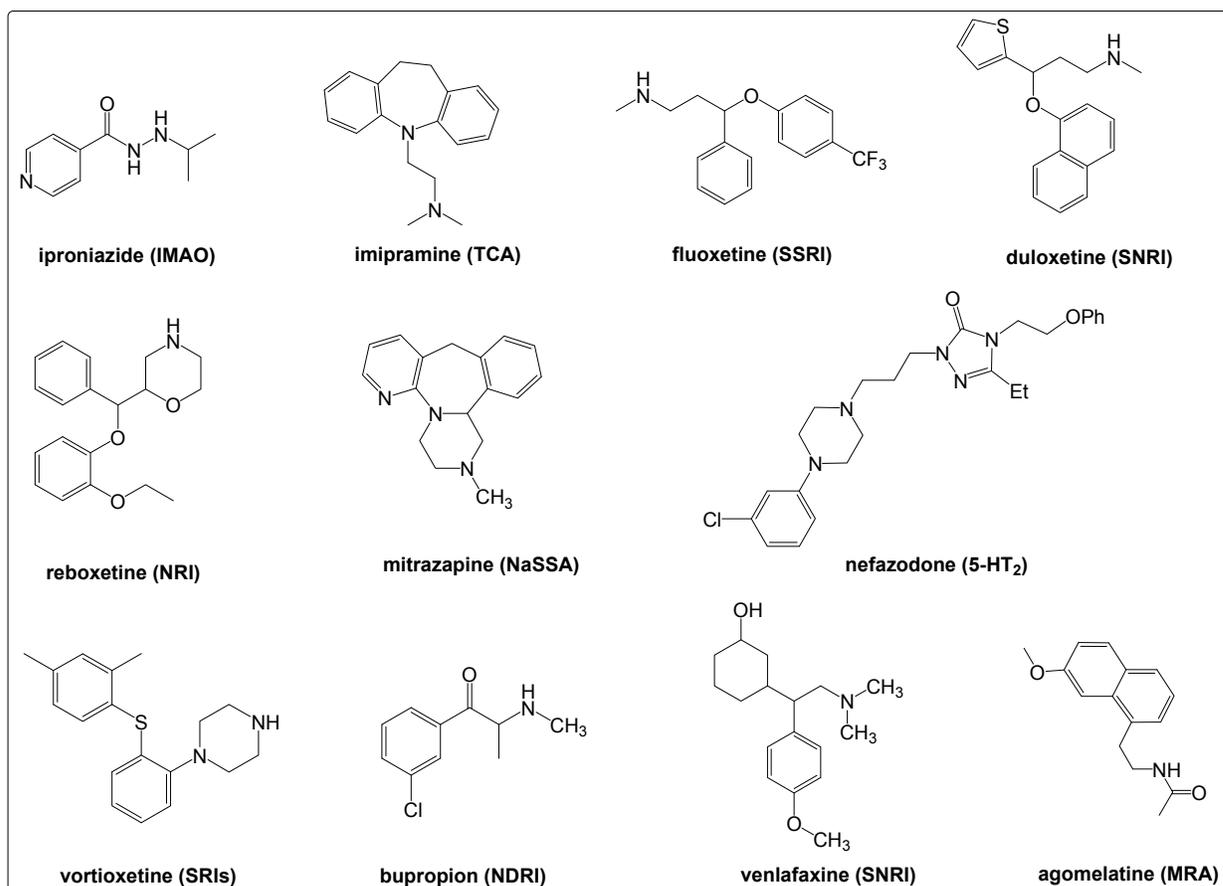


Fig. (2). Chemical Structure of Representative Antidepressants Agents.

EP2026793A2 (2009) [13] and sertraline (patent number US 7186863 B2 [14]), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine (patent number WO2007039569 [15]), desvenlafaxine (patent number WO2010028130 [16]), milnacipran (patent number WO2005118564 [17]) and duloxetine (patent number US 8513439 B2 [18]), selective norepinephrine reuptake inhibitors (NRIs; reboxetine (patent number EP 1515959 B1 [19]), noradrenergic and specific serotonergic antidepressants (NaSSAs; mirtazapine (patent number EP99917956 [20]) and mianserin (patent number EP 1017695 A1 [21]), and 5-hydroxytryptamine type 2 (5-HT<sub>2</sub>) receptor antagonists (nefazodone (patent number US 5256664 A [22-24]). Certain representatives of novel antidepressants have gained special attention since they have shown a higher efficacy in severe depression [25]. However, their biological activity affects a number of neurotransmitter systems (dopamine reuptake inhibition, norepinephrine reuptake inhibition, serotonin correlation); consequently their usage might affect cardiovascular system. There is strong evidence that patients with major depressive disorder (MDD) are at increased risk of developing coronary heart disease (CHD) and arterial hypertension [26]. Despite the issuing of antidepressants for patients correlates with cardiovascular diseases, the choice of the suitable drug appears as a major question for reflection.

## ANTIDEPRESSANTS DRUGS

### SSRIs and the Cardiovascular System

Available data suggest that the older antidepressants such as the TCAs may increase the risk of mortality especially in patients with ischemic heart disease [27]. Their common adverse cardiovascular effects are increase in heart rate, hypotension and conduction delays. On the other hand, SSRIs have a relatively benign cardiovascular profile. Therefore, they are preferable for treatment of depression in patients who have high cardiovascular risk.

Fluoxetine [7] (also known by the tradenames Prozac, Sarafem, and Fontex, etc) is one of the most popular agents in SSRIs class. It was first presented to the U.S Food and Drug Administration in 1977, with Eli Lilly receiving final approval to market the drug in 1987. 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). There is no clinical evidence of conduction delay and very little evidence of orthostatic hypotension [28]. In the overdosed patients fewer cardiac symptoms were reported than with TCAs. However, atrial fibrillation, bradycardia and syncope associated with fluoxetine treatment and overdose were reported [29].

Kobayashi and coworkers have shown that novel antidepressants, particularly SSRIs are G protein-activated inwardly rectifying K<sup>+</sup>(GIRK) channels (also known as Kir3 channels), channel modulators that may affect various brain and cardiac functions [30]. In the heart, GIRK channels cause a slowing of heart rate in response to activation of M2 muscarinic receptors through acetylcholine release from the stimulated vagus nerve [31]. GIRK1 and GIRK4 knockout mice exhibit slightly elevated resting heart rates. This might

be implicated in the arrhythmic adverse events in patients receiving toxic doses of SSRIs.

However, clinical studies have shown favorable data for the use of SSRIs regarding the cardiovascular system. 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 [28]. They also found that antidepressants suppress IFN- $\gamma$  production [32]. Cohen *et al.* have shown that there is a significant autonomic dysregulation at rest in posttraumatic stress disorder patients, which is corrected by treatment with fluoxetine [25]. Lekakis *et al.* have proved that SSRIs may exhibit an anti-inflammatory activity on endothelial cells and reduce circulating VCAM-1 and ICAM-1 *in vivo*, a mechanism which may partly mediate their cardioprotective effects [33].

Depression and hostility are significant risk factors for mortality and morbidity after myocardial infarction. Fluoxetine seemed to be particularly effective in patients with mild depression after myocardial infarction and was associated with a statistically significant reduction in hostility [34].

In addition, SSRIs might decrease the risk of ischemic heart disease events by blocking the uptake of serotonin into platelets, leading to impairment in the platelet hemostatic response. On the other hand, this is the mechanism affecting the hemostasis and increased bleeding that may be observed in those patients especially on top of antiplatelet therapy. In a retrospective cohort study in 27,058 patients, an increased risk of bleeding was found in patients taking an SSRI together with ASA or dual antiplatelet therapy following acute myocardial infarction [35]. Notably, a pronounced inhibition of metoprolol metabolism by paroxetine was observed in AMI patients, but without serious adverse effects. It is suggested, however, that the metoprolol dose is controlled upon initiation and withdrawal of paroxetine [36].

SSRIs as other psychotropic drugs often induce weight gain. The phenomenon is more prominent with paroxetine while the effect of fluoxetine appears to be limited in the acute phase of treatment [37]. Another study aimed to describe the effects of SSRIs on the metabolic parameters of drug-naive first episode patients with generalized anxiety disorder which included 97 female patients aged 20-41 years without any metabolic or psychiatric comorbidity. Fluoxetine, sertraline, paroxetine, citalopram and escitalopram were randomly given to the patients. Metabolic parameters, including BMI, waist circumference and the levels of fasting glucose, total cholesterol, triglyceride, HDL, LDL and blood pressure, were measured before and after 16 weeks of treatment [38]. In the paroxetine group, there was a significant increase in the parameters of weight, BMI, waist circumference, fasting glucose, total cholesterol, LDL and triglyceride after 16 weeks of treatment. There were significant increases in the levels of triglyceride in the citalopram and escitalopram groups. In the sertraline group, the total cholesterol level increased after treatment. In the fluoxetine group, there were significant reductions in the parameters of weight, total cholesterol and triglyceride [34].

Finally, SSRIs and more specifically antenatal exposure of fluoxetine during pregnancy was associated with an increased risk of cardiovascular malformation [39]. In general,

SSRIs such as fluoxetine, paroxetine, sertraline and citalopram are considered to be free from the cardiotoxicity of their predecessors and be safe in terms of platelet activation, atherosclerosis and coronary heart disease.

#### **BUPROPION: A DOPAMINE-NOREPINEPHRINE REUPTAKE INHIBITOR (PATENT FORM WO 2007060540 A1 [40])**

SSRIs are generally recommended as first-line therapies for depressed patients with heart failure. If SSRI therapy is not well tolerated or adjunctive therapy is required, bupropion, mirtazapine, venlafaxine, and duloxetine may be suitable alternatives for certain patients [41].

Bupropion had gained a lot of widespread use and it was also marketed in lower doses (Zyban, Voxra) as a drug to reduce nicotine cravings by people who are trying to quit smoking. It is a dopamine as well as a norepinephrine reuptake inhibitor and releaser [42]. The primary pharmacological action of bupropion is a mild dopamine reuptake inhibitor and also a much weaker norepinephrine reuptake inhibitor as well as a nicotinic acetylcholine receptor antagonist [38]. With regard to medical viewpoint, bupropion serves as a non-tricyclic antidepressant fundamentally different from most commonly prescribed antidepressants such as SSRIs. Bupropion was patented in 1969 by Burroughs Wellcome and it was originally called amfebutamone. It received US patent in 1974, and was approved by the United States Food and Drug Administration (FDA) as an antidepressant in 1985. In contrast to other antidepressants, it does not cause weight gain or sexual dysfunction [43, 44]. A dose-dependent risk of seizure was the cause of a temporary withdrawal from the market between 1986 until 1989. In addition, bupropion is used as antismoking therapy and appears to be safe in hospitalized patients with acute cardiovascular disease [45].

Due to the pathophysiological action of bupropion, a lot of reflections existed from the beginning with regard to its effect in the arterial pressure. The above reflection became more powerful after a range of clinical trials in dogs, where it induced an increase in the medium arterial pressure as well as in the pressure of the lung artery [46]. Previous studies have indicated its potential increase in heart rate and hypertension in adults [47]. Even if the first clinical trials indicated an increase arterial pressure, however it was reported that the drug remains safe in patients with arrhythmias [48]. Nevertheless, a moderately prolonged QTc (>440 msec) is common in bupropion overdose. This may not be a result of intrinsic cardiac toxicity, but overcorrection of the QTc due to the tachycardia that occurs [49].

In a meta-analysis in more than 500 patients with depression, bupropion sustained-release (SR) 100–400 mg had no significant effects on BP or heart rate compared with placebo [50]. Another study compared the hemodynamic effects of short-term (7 days) bupropion (150 mg daily for 6 days, then 300 mg once) in patients quitting smoking [51]. The maximal increases in the SBP were 17/12 mm Hg for SBP and DBP respectively in bupropion group which did not differ significantly in the control group. The drug also appears to be safe in cardiovascular patients as trials conducted for smoking cessation have indicated. No more cardiovascular

adverse effects were reported in those patients until one year after the initiation of the drug [52].

In a randomized study the effects of bupropion on blood pressure and heart rate were evaluated in 300 community volunteers with untreated mild (stage 1) hypertension. These and coworkers demonstrated that only minor effects on blood pressure were observed in this trial, as a consequence, an infrequent association of bupropion therapy and treatment-emergent hypertension cannot be ruled out [53]. Another concern we should keep in mind is that bupropion is metabolized in liver by the cytochrome CYP2B6, creating conditions for likely interaction with cardiologic medicines. As recommended in the prescribing information, beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication [49]. Many studies also indicate that bupropion is safe in few cardiovascular diseases; however, more research is required in order to establish its effects in cardiovascular system following their chronic use [54].

#### **SNRIs AND THE CARDIOVASCULAR SYSTEM**

The first SNRI was venlafaxine [12], which was introduced into the US clinical practice in 1994. Additionally, SNRI family includes desvenlafaxine, as well as two structurally unrelated compounds milnacipran and duloxetine. Many of the side effects of venlafaxine that are presumed to be mediated by norepinephrine reuptake inhibition, including dizziness, dry mouth, increased pulse and increased sweating, show similar dose-dependence. Similarly, the effects of venlafaxine on blood pressure are presumed to be at least partly mediated by norepinephrine reuptake inhibition, are strongly dose-dependent, and at minimum therapeutic dose (75 mg/day) the effects of venlafaxine on blood pressure are similar to those of placebo [55]. Venlafaxine appears to be more toxic than other novel antidepressants and overdose is accompanied commonly with cardiac toxicity, mostly QT prolongation [56]. Very often, it is associated with QT prolongation and the patient requires cardiac monitoring and arrhythmias [57]. This may pose an arrhythmogenic risk, despite this was not confirmed in the studies. In parallel, caution is needed since venlafaxine high doses or overdose is associated with cardiac toxicity. Severe and diffuse left ventricular dysfunction may be observed after large venlafaxine overdoses that are sometimes associated with severe cardiac conduction function abnormalities [58]. The mechanisms underlying venlafaxine-related cardiac failure with preserved normal cardiac conduction are discussed. A possible explanation may be a catecholamine-induced myocardial damage in relationship with the inhibition of norepinephrine (and dopamine) reuptake. In addition, cases of Takotsubo cardiomyopathy have been described in association with therapeutic ingestion or overdose of the serotonin/noradrenaline reuptake inhibitor venlafaxine, or its metabolite desvenlafaxine [59].

Milnacipran was the second SNRI to be introduced. Milnacipran is a more potent inhibitor of norepinephrine reuptake at minimum therapeutic doses and may require upward titration in order to affect significant inhibition of serotonin

reuptake in the central nervous system. Milnacipran is considered a relatively safe antidepressant agent without significantly affecting cardiac repolarization at clinically relevant therapeutic and supratherapeutic concentrations or blood pressure [60]. It is reported that hypertension, tachycardia and reversible cardiomyopathy are temporally associated with milnacipran use in rare cases [61].

Duloxetine [15], which was introduced in the US in 2004, is promoted by the manufacturer as a "balanced" SNRI. Duloxetine is a significantly more potent norepinephrine reuptake inhibitor than venlafaxine and a significantly more potent serotonin reuptake inhibitor than milnacipran. Consequently, duloxetine therapy acts on both neuronal systems at the minimum therapeutic dose and, as such, might require less titration to achieve optimum therapeutic effect than either milnacipran or venlafaxine [62]. It is noteworthy that, despite more potent inhibition of norepinephrine uptake than venlafaxine, duloxetine therapy is not associated with increased rates of treatment-emergent high blood pressure. Cardiovascular safety was evaluated based on vital signs, ECGs and the incidence of treatment-emergent adverse effects potentially related to cardiovascular safety [63, 64]. Calculation of change from baseline to maximum in ECG parameters showed significant differences between treatment groups for all parameters, with decreases from baseline in RR, QRS and QT intervals for patients receiving duloxetine and increases from baseline for patients treated with placebo. These shifts were related to small heart rate changes, but the mean differences were not considered clinically relevant. Patients who were treated for up to 1 year with duloxetine had blood pressure changes early in treatment that then stabilized. Even in patients with elevated blood pressure at baseline in these clinical trials, no increased risk of sustained blood pressure elevation with duloxetine treatment was found [60]. Overall, the findings revealed that the use of duloxetine does not appear to be associated with significant cardiovascular risks in patients with conditions for which the drug has been approved or studied. Similarly, there is no evidence for an increased risk of cardiovascular or cerebrovascular events associated with desvenlafaxine up to 100 mg daily dose.

#### **OTHER PHARMACOLOGICAL CATEGORIES OF ANTIDEPRESSANTS AND THE CARDIOVASCULAR SYSTEM**

Mirtazapine [17] (Remeron, Avanza, Zispin) is a NaSSA which was introduced by Organon International in 1990. A study conducted in 2177 patients with myocardial infarction and depression who randomized to mirtazapine vs. placebo, other antidepressants or no pharmacological treatment, showed no improvement in depression compared with usual care and had no effect on cardiac event rate at 18 months [65]. Nevertheless, a follow up study showed that the response to treatment was protective from cardiovascular events, however, the use of mirtazapine requires huge attention due to its significant orthostatic hypotension side effects [66]. In a similar way, mianserin can lead to bradycardia and hypotension mostly in cases of intoxication; that is why mianserin treatment needs close monitoring [48, 67].

Reboxetine [16] is a drug of the norepinephrine reuptake inhibitor class (NRIs) developed by Pharmacia (now Pfizer) and appears on the market named under tradenames including Edronax, Norebox, Prolift, Solvex, Davedax or Vestra. It is approved for use in many countries worldwide, but has not yet been approved for use in the United States. Reboxetine is a well tolerated agent which seems to be beneficial in metabolic parameters (such as cholesterol, HDL- and LDL-cholesterol, triglycerides, free fatty acids) independently from treatment outcome [68]. However, it might influence the distribution of sympathetic activity between the heart, vasculature, and kidney in humans as a consequence that might lead to corresponding changes in organ function. More specifically, in a study in healthy individuals, 8mg of reboxetine increased supine systolic blood pressure through an increase in cardiac output whereas systemic vascular resistance decreased. Additionally, reboxetine increased heart rate while decreasing plasma renin activity and plasma angiotensin II concentrations [69].

In general, noradrenergic antidepressants (NAs) like mirtazapine and mianserin and 5-HT<sub>2</sub> antagonists like nefazodone typically cause minor changes in blood pressure and heart rate and noradrenergic actions do not seem to have a risk of death in overdose [62, 63].

#### **AGOMELATINE: THE FIRST MELATONERGIC ANTIDEPRESSANT [70].**

Agomelatine (Valdoxan, Thymanax, Novartis) is a melatonergic (MT<sub>1</sub> and MT<sub>2</sub>) receptor agonist and a complementary 5-hydroxytryptamine 2C receptor antagonist, which treats depression by resynchronizing the circadian rhythms that are profoundly disturbed in depressed patients [71]. Circadian malfunction is a core feature of depression and disruption of circadian rhythms in depressed patients affecting mood, behavior, and physiological and biological functions [72]. Agomelatine has demonstrated antidepressant efficacy against placebo in the short and long term, irrespective of disease severity, and has also outperformed venlafaxine and sertraline on several rating scales, especially those reflecting clinical practice [73]. Animal studies suggest a possible neuroprotective action of agomelatine, although there are more data in favor of an anxiolytic effect. Agomelatine appears to be well tolerated, without sexual or cardiac adverse effects, weight gain or discontinuation syndromes [74]. These features make it a truly novel approach to depression, providing early symptomatic relief within a framework of complete and sustained remission.

#### **RECENT PATENTS AND FUTURE PERSPECTIVES**

Antidepressant response rates in controlled trials are estimated at ~54 % and real-world effectiveness data might be at a lower rate especially in patients who have not responded to previous treatments [75]. So, the need for novel antidepressants is still needed. Due to the limited antidepressive effects of SSRIs and SNRIs combination therapies have been introduced such as venlafaxine plus bupropion [76], SSRIs plus pindolol [77], or SSRIs augmented with atypical antipsychotics such as aripiprazole [78] which their additive effects of which on cardiovascular system have not been extensively studied. A close, bidirectional relationship exists

between depression and cardiovascular disease. Major depression is associated with an increased risk of coronary artery disease, congestive heart failure and myocardial infarction leading to increased mortality and morbidity in patients [79].

## CURRENT & FUTURE DEVELOPMENT

The future generation of antidepressants should have fewer side effects which are the most common cause of discontinuation, in particular sexual dysfunctions and weight gain [80, 81]. Weight gain, even if is not considered as side effect related directly to the heart, in the future it may lead to adverse cardiovascular events. So far, vortioxetine (Lu AA21004, Brintellix and Rexulti) is an experimental drug currently under development by Lundbeck and Takeda for the treatment of major depressive disorder and generalized anxiety disorder. Regulatory approval for the treatment of major depressive disorder for the European market has been filed in September 2012, for the United States in October 2012, and filing for Canada should follow. Filing for the Japanese market is expected in 2013 [82]. Vortioxetine combines serotonin (5-HT) reuptake inhibition, receptor activity modulation and neurotransmission effect (noradrenaline, dopamine, acetylcholine, histamine in certain areas of the brain as well as modulating  $\gamma$ -aminobutyric acid and glutamate) [83]. No significant cardiovascular effects are revealed for this agent; however randomized studies are needed to enlighten these questions. Future research involves the investigation of the central neuropeptides, including substance P, corticotrophin releasing factor, neuropeptide Y, vasopressin and oxytocin, galanin and melanin-concentrating hormone [75, 80-83]. However, data are controversial and no one of these agents has reached clinical practice.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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