Abnormal function of monoamine oxidase-A in comorbid major depressive disorder and cardiovascular disease: Pathophysiological and therapeutic implications (Review)

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Abstract. The association between major depressive disorder (MDD) and cardiovascular disease (CVD) is among the best described medical comorbidities. The presence of MDD increases the risk of cardiac admissions and mortality and increases healthcare costs in patients with CVD, and similarly, CVD affects the course and outcome of MDD. The potential shared biological mechanisms involved in these comorbid conditions are not well known. However, the enzyme monoamine oxidase-A (MAO-A), which has a key role in the degradation of catecholamines, has been associated with the pathophysiology and therapeutics of both MDD and CVD. Increased MAO-A activity results in the dysregulation of downstream targets of this enzyme and thus affects the pathophysiology of the two diseases. These deleterious effects include altered noradrenaline turnover, with a direct elevation in oxidative stress parameters, as well as increased platelet activity and cytokine levels. These effects were shown to be reversed by MAO inhibitors. Here, a model describing a key role for the MAO-A in comorbid MDD and CVD is proposed, with focus on the shared pathophysiological mechanisms and the potential therapeutic relevance of agents targeting this enzyme.

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1. Introduction

Comorbid major depressive disorder and cardiovascular disease: general aspects. Major depressive disorder (MDD) is a serious, recurrent, prevalent and disabling psychiatric illness affecting millions of individuals worldwide, which presents a negative impact on medical health and productivity (1). Similarly, an estimated 80 million Americans have at least one form of cardiovascular disease (CVD) (2).

The association between MDD and CVD is among the best described medical comorbidities (3). Early epidemiological studies showed that the age-adjusted mortality rate in depression was approximately 6 times higher than in the general population, with almost half of these cases directly related to 'diseases of the heart' (4). Recent studies showed that around 1/5 of subjects recently diagnosed with CVD also have MDD (5-7). Despite being well documented, MDD remains underdiagnosed in patients with CVD and presents a direct negative impact on the course and outcome of CVD (8). For instance, the presence of depressive symptoms significantly enhances the risk of cardiac admissions and mortality, also increasing healthcare costs in patients with a cardiac disease (9).

Furthermore, according to a recent survey, 50% of cardiologists were unaware of MDD as an independent risk factor for CVD and 71% address the potential presence of MDD in less than half their patients with CVD. In total, 79% do not use any standard screening method to diagnose depression (10). Thus, the assessment of this comorbidity in clinical practice and the study of its potential biological variables may

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potentially help in the development of new, improved treatments able to treat the two conditions concomitantly.

Comorbid MDD and CVD: is there a primary and secondary condition? More than 100 studies have evaluated the potential association between MDD and CVD, showing that depression is more prevalent (20-35%) in populations with any CVD (11). Clearly, MDD has been associated with an increased incidence of cardiac disease and worsens the prognosis in patients with known coronary heart disease (e.g., doubling the risk of cardiac events) (9). Recently, Ellis *et al* (12) described that 41.2% of 490 subjects with an acute coronary event present depressive symptoms, while only 10% of them were adequately treated with antidepressants and/or psychosocial support.

It has been proposed that the majority of coronary disease follows rather than precedes MDD, but it may be considered that previous environmental and/or genetic factors can lead to biological changes in the brain and periphery that may give rise to the two conditions (13). By contrast, certain authors suggest that MDD induces specific biological changes centrally that could increase the risk of CVD (13). Another possibility is that the association of MDD and CVD is indirect. For example, there is evidence that depressed patients are less likely to comply with treatments for cardiovascular conditions (14). It has also been proposed that altered circadian rhythms described in mood disorders may disrupt cardiovascular physiology, such as heart rate and blood pressure, thus increasing the risk for adverse cardiac events, such as heart attack and stroke (15).

Evidence for MDD as a primary condition. Convincing evidence has suggested a key role for MDD in the onset and course of CVD. First, the risk of CVD is clearly higher in subjects with MDD (16). Diverse meta-analyses have described effect sizes for MDD in the development of coronary heart disease from ~1.5 to 2.7 (3,17-19). For instance, subjects presenting a depressive episode at the time of an acute myocardial infarction (MI) have a significant increase in mortality rates compared to those not in a depressive episode (20). Specifically, changes in depressive symptoms (21) or a new episode of MDD (22) enhance the risk of coronary events rather than chronic depressive symptoms. Depressive symptoms such as insomnia have also been associated with increased risk of MI (23) and cardiac mortality (24). These effects appear to involve several pathophysiological effects in MDD that may be directly connected to the arousal of adverse cardiac outcomes (25,26).

Evidence for CVD as a primary condition. MDD has been considered an independent risk factor for CVD (20). In patients with coronary heart disease, size effects for the prediction of MDD range between 1.6 and 2.2 (18,27,28). Notably, it was shown that following MI, more than 20% of all patients met criteria for MDD (29). Regarding potential indirect associations, many cardiovascular drugs are capable of inducing depressive symptoms, such as β-blockers, methyldopa and reserpine (30).

Overall, the evidence supports a role for both MDD and CVD as the primary condition in this comorbidity, with more consistent data for MDD increasing risk for CVD.

2. The role of monoamine oxidase-A in the pathophysiology and therapeutics of MDD

Monoamine oxidases: general aspects. Monoamine oxidases (MAOs) are mitochondrial flavoenzymes that catalyze oxidative deamination of dietary amines, monoamine neurotransmitters and hormones, including indoleamines [serotonin (5-HT) and tryptamine] and catecholamines, such as norepinephrine (NE), epinephrine and dopamine (DA) (31). Thus, MAO is responsible for the metabolism of biologically active amines. The process of oxidative deamination of these amines results in removal of the amino functional group to leave an oxidized oxygen, thus generating the toxic products ammonia (NH_3) and hydrogen peroxide (H_2O_2) (32). H_2O_2 is a key mediator in the production of the most potent free oxygen radicals, namely the hydroxyl radical (OH·) (33), which induces deleterious effects in several organs, particularly the brain.

Two isoforms of MAO have been identified, designated types A and B, which have distinct substrate affinity and inhibitor sensitivity (34). MAO-A is the major form of this enzyme found in the periphery. In the brain, MAO-A is mostly found in outer mitochondrial membranes in noradrenergic neurons, while MAO-B has been observed in glial cells and 5-HT/histaminergic neurons (35). The ratio of MAO-A to MAO-B in the human brain is 25/75%, even though MAO-A inhibitors have shown superior antidepressant effects (36). In fact, inhibition of MAO-A is thought to be the action most directly linked with the antidepressant activity of the MAO inhibitors (37). MAO-A preferentially metabolizes NE and 5-HT, the monoamines most closely linked to depression, while MAO-B preferentially metabolizes trace amines, including phenethylamine (38). The degradation of biogenic amines by MAO-A has been considered the major physiological function of this enzyme.

MAO-A in the pathophysiology and therapeutics of MDD. The primary role of MAO-A is to regulate monoaminergic turnover and levels. Elevated MAO-A levels may be expected to metabolize NE and 5-HT more extensively (34), thus resulting in relative monoamine depletion.

This effect may be critical in the pathophysiology of MDD. MAO-A regulates the levels of NE by catalyzing its oxidative deamination (31). The increased sympathoadrenal system activity observed in MDD has been associated with enhanced excretion of NE, epinephrine and dopamine (39). Similarly, patients with MDD are reported to have increased plasma NE levels, increased heart rates and reduced heart-rate variability (40). Regarding the potential role of MAO-A in the pathophysiology of MDD, it was recently described that unmedicated subjects with MDD show greater depletion of previously synthesized stores of 5-HT, along with higher levels of 5-hydroxyindoleacetic acid (5-HIAA) (41). 5-HIAA is produced by intraneuronal deamination of 5-HT (via MAO-A).

In regard to the 5-HT regulation by MAO-A, in the tryptophan depletion challenge, mood lowering effects were more prevalent in unmedicated euthymic subjects with a history of MDD as compared to healthy controls (42-45). Higher MAO-A levels may explain the increased vulnerability to tryptophan depletion in MDD patients in recovery through excessive metabolism of 5-HT by MAO-A, which would facilitate

loss of extracellular 5-HT. By contrast, selective serotonin reuptake inhibitors (SSRIs) decrease 5-HIAA production by blocking neuronal 5-HT reuptake, which elevates 5-HT levels substantially (46). Notably, SSRIs were also shown to reverse different dysfunctions associated with the pathophysiology of MDD and CVD, such as altered urinary cortisol excretion and heart rate variability, as well as enhanced platelet activation and increased inflammatory marker levels (47-49).

Since MAO-A is involved in the removal of multiple monoamines, increased MAO-A binding in MDD may be involved in the potential mood-lowering effects following depletion of NE with α-methylparatyrosine administration (50,51), as well as having a potential association with increased risk of recurrence of MDD (52).

Increased MAO-A density in several brain areas has been considered an important monoamine-lowering process during depressive episodes in MDD (52,53). A previous PET study using carbon 11-labeled harmine (a tracer with high affinity to MAO-A) showed an abnormal increase in MAO-A binding during depressive episodes (53). A subsequent PET study evaluated 28 healthy subjects, 16 subjects with MDD in a depressive episode and 18 subjects with MDD in recovery prior to and following 6 weeks of SSRI treatment, followed up for 6 months after MAO-A binding quantification. The authors demonstrated a significant increase in MAO-A density during a depressive episode compared with healthy controls, which remained elevated following treatment with SSRIs (52). Although brain MAO-A density was generally enhanced during recovery, patients who experienced depressive recurrence showed significantly higher MAO-A density in the prefrontal and anterior cingulate cortex as compared to those who did not (52). Based on these findings, it was proposed that higher MAO-A binding (and density) may be considered a trait marker in MDD. It was also found that the regional density of MAO-A transporters has a selective influence on particular monoamines, with a direct association with specific clinical presentation (53). A recent study showed that the MAO-A total distribution volume was significantly elevated (by a mean of 43%) in different brain regions during the early postpartum period, indicating that this monoamine-lowering process contributes to the mood change in postpartum blues (54).

Given that an abnormal increase in MAO-B density is less expected to occur in MDD, the present results appear to be specific to MAO-A. For instance, a postmortem study described no significant difference of MAO-B density in the amygdala of subjects with MDD (55).

Regarding genetic studies, MAO-A (located at Xp11.3) has been considered an important candidate gene in mood disorders. Besides being considered as a potential risk gene in depressed suicidal patients (56), it has been associated with specific psychological traits (57). Studies also suggest that MAO-A gene alleles associated with higher transcriptional efficiency predispose to dysfunctional behavior such as trait aggressiveness and impulsivity (58,59). Three common polymorphisms that critically affect transcriptional efficiency have been evaluated in association studies on the MAO-A gene in mood disorders: i) a promoter variable number tandem repeat polymorphism (uVNTR) (60,61); ii) a G/T polymorphism at position 941 of the cDNA sequence, which is a silent mutation in exon 8 (62); and iii) a dinucleotide repeat in intron 2

(MAOA-CA) (63). Significant associations between these three common polymorphisms have been demonstrated in meta-analyses evaluating case-control association studies in MDD (64,65). MAO-A knockout mice have increased brain NE and 5-HT levels (66). The consequent decrease in MAO-A levels improved resilience and adaptation to the effects of environmental stressors, which is also associated with antidepressant-like effects (66).

It is important to note that the MAO-A metabolism increases oxidative stress levels (34), which have been directly involved in the pathophysiology of MDD (67). The dysregulation of redox balances and mitochondrial damage induced by MAO activation may result in neuronal apoptosis and brain damage. For instance, serum-starvation-induced apoptosis increases MAO-A levels, which was prevented by using an MAO-A inhibitor in cortical neurons (68). Neurodegenerative toxicity and striatal lesions induced by malonate were significantly and selectively attenuated by MAO-A inhibitors and in MAO-A KO, without a positive response to a MAO-B inhibitor (69).

Regarding the therapeutic potential of specific MAO-A inhibitors for MDD, the clinical efficacy of diverse reversible inhibitors of MAO (including specific MAO-A inhibitors or RIMAs) has been observed in treatment-resistant depression (70), mostly related to inhibition of MAO-A (38). However, it is important to emphasize that the majority of the currently available MAO inhibitors are non-selective, inhibiting MAO-A and MAO-B (38).

3. The role of MAO-A in the pathophysiology and therapeutics of CVD

Monoaminergic neurotransmitters have a critical functional role in the heart, including the regulation of cardiac inotropy (13). Increased catecholamine metabolism and altered tissue distribution regulated by MAO have been directly associated with the aging process (71,72). MAO-A is present in the myocardium of diverse species from rodents to humans (73,74). The heart contains a large amount of MAO-A (75,76) and its role in the regulation of cardiac function critically involves NE concentrations (77,78).

It was recently shown in preclinical models that NE is capable of triggering CVD in a MAO-A-dependent manner (79). NE catabolism and ROS production are markedly upregulated in pressure-overloaded hearts and both effects are ameliorated by limiting MAO-A activity to suppress cardiac decompensation with pressure overload (79). Similarly, increased sympathetic activity in the central nervous system (CNS) with concomitant elevated levels of catecholamines has also been proposed as one potential mechanism by which depressive symptoms may increase CVD morbidity and mortality (80). MAO-A is also an important source of hydrogen peroxide (H_2O_2) in the heart (81). MAO-A plays a key role in reactive oxygen species-dependent cardiomyocyte apoptosis and postischemic cardiac damage (82). Elevated mitochondrial oxidative stress levels and/or decreased mitochondrial antioxidant defenses have been shown to aggravate atherosclerosis (83). MAO-A mediates reactive oxygen species (ROS)-induced activation of mitogenic signaling in endothelial cells related to vascular wall remodeling (associated with

atherosclerosis), which were inhibited by the MAO-A inhibitors pargyline and Ro41-1049 (84).

The involvement of MAO-A and its impact on neurotransmitter availability in congestive heart failure (CHF) has also been shown. In preclinical models, left ventricular dilation and pump failure attributable to pressure overload have been associated with increased NE catabolism by MAO-A, with enhanced production of free radicals and myocardial apoptosis. MAO-A activity worsens the disease progression (13). CHF is directly associated with an increased sympathetic tone and altered oxidative stress parameters (85). In such situations, MAO-A may be upregulated, generating greater amounts of H_2O_2, and thus exacerbating disease progression. The increased oxidative stress induced by MAO-A has also been directly associated with postischemia-reperfusion apoptosis (76). Notably, inhibition of MAO-A by clorgyline ameliorated the majority of these changes (79).

The cardioprotective effects of MAO inhibitors are associated with the prevention of postischemic oxidative stress, neutrophil accumulation and mitochondrial-dependent cell death (76), thus inducing positive effects in myocardium reperfusion. The inhibition of MAO-A *in vivo* largely reduced myocardial ultrastructural damage following ischemia. Diverse MAO inhibitors (JB-516, JB-835, RO-50700, harmine, harmaline and iproniazid) have been shown to increase heart contractile force through effects induced by norepinephrine, dopamine, tryptamine, tyramine and serotonin in animals (86).

4. Increased MAO-A activity as a factor linking depression with comorbid cardiac disease

Here we describe a model integrating various pathophysiological findings and targets directly associated with the effects of MAO-A with a potential key relevance to the shared pathophysiology of comorbid MDD and CVD. Enhanced sympathetic CNS activity mediated through MAO-A is here proposed as a potential common mechanism for the development of MDD and cardiac morbidity, potentially by concomitantly increasing oxidative stress levels, activating immuno-inflammatory responses and enhancing glucocorticoid metabolism, as described below (Fig. 1).

NE activity. As mentioned previously, MAO-A critically controls brain and peripheral NE levels by regulating the oxidative deamination of NE (38). In preclinical models, the induction of a MAO-A-dependent NE overflow and elevated breakdown has been shown to be a key factor in the etiology of CVD; these dangerous downstream effects were stalled by using the selective MAO-A inhibitor clorgyline (79). Similarly, CVD has also been associated with alterations in autonomic balance. Elevated sympathetic tone, as measured by plasma NE, predicts mortality in CVDs, such as left ventricular dysfunction and chronic CHF (87). Specifically, elevated NE levels in patients with CHF have been positively correlated with severity of symptoms and mortality. Similarly, higher NE excretion was associated with lower left ventricular ejection fraction (88). NE levels also predict mortality after MI (89). Notably, depressive symptoms in patients with CVD were associated with elevated levels of NE excretion but not DA (90). Importantly, the oxidative deamination of NE by MAO-A
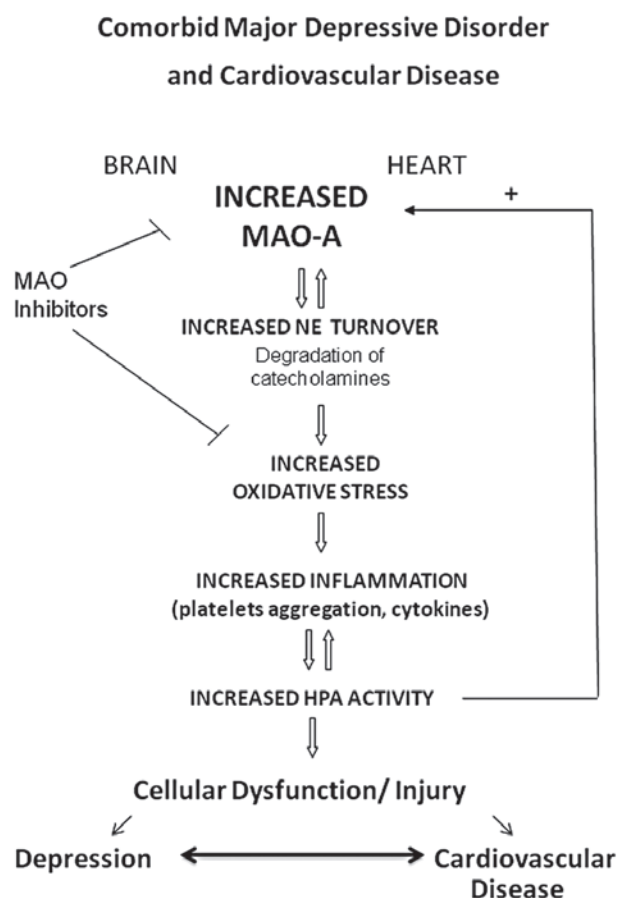

Figure 1. Integrative biological model explaining the key role for MAO-A in comorbid depression and cardiovascular disease: involvement of oxidative stress, inflammation and glucocorticoid activity. MAO-A, monoamine oxidase-A; NE, norepinephrine.

increases ROS and oxidative stress levels by releasing reactive aldehydes and H_2O_2 (as described below).

At the same time, increased sympathetic activity in the CNS with concomitant elevated levels of catecholamines turnover has also been proposed as one potential mechanism by which depressive symptoms may increase morbidity and mortality (80). The increased sympathoadrenal system activity observed in MDD has been associated with enhanced excretion of NE, epinephrine and DA (39). Patients with MDD presented with increased heart rates and reduced heart-rate variability, reflecting altered cardiac autonomic tone (40).

Oxidative stress parameters. Increased oxidative stress parameters have been described in the pathophysiology of MDD in several studies (reviewed in ref. 67). For instance, individuals in a depressive episode have significantly lower total antioxidant potential and higher oxidative stress levels compared to healthy controls (91). Diverse studies have also shown an inverse association between severity of depressive symptoms and oxidative stress levels (92-94). Increased oxidative damage and apoptosis in cortical neurons are associated with elevated MAO-A, and may be potentially prevented by using MAO-A inhibitors (68).

Similarly, CVD is directly related to increased oxidative stress levels (95). Consistent evidence from basic research

studies suggests that reactive oxygen species contribute to atherosclerosis and CVD (96). For instance, reactive oxygen species are also capable of stimulating matrix metalloproteinases, which contribute to atherosclerotic plaque instability and rupture, thus inducing acute coronary syndromes (97). MAO-A is a recognized source of ROS (76,79). These effects may involve MAO-A, since this enzyme is an important source of mitochondrial H_2O_2 in the heart, thus contributing to oxidative stress-induced cardiomyocyte apoptosis (76).

Immune-inflammatory activation. Growing evidence has shown a significant increase in immune-inflammatory markers in MDD (98), which have been directly involved in the increased production of ROS and oxidative stress levels (99,100). At the same time, ROS may also induce LDL oxidation and activation of vascular smooth muscle cell proliferation and migration, as well as increase the production of proinflammatory cytokines (96). Pasic *et al* (101) described several findings on immune-inflammatory changes in MDD and CVD, indicating that cytokines may provide a new avenue in understanding brain-body interactions in MDD and CVD.

MAO-A activates inflammatory cascades and platelet activity, with consequent endothelial dysfunction. Platelets adhere to intact endothelial cells and promote local vascular inflammation by recruiting leukocytes via direct interaction or by activating inflammatory mediators (102). Platelets share similar biochemical processes with neurons; platelet MAO activity was found to be related to central monoamine turnover, although platelets express mainly MAO-B. Platelets are also thought to play a predominant role in the initiation and progression of atherogenesis (103). Notably, MAO-A expression was shown to be significantly increased by pro-inflammatory cytokines in human monocytes (104). MAO-A substrates, such as 5-HT and NE, may act as vasoactive mediators at inflammatory sites (104). These data support a role for MAO-A in the inflammation-inducing CVD dysfunction.

Similarly, patients with significant depressive symptomatology have altered endothelial function compared to non-depressed individuals; the use of monoaminergic antidepressants is associated with reversal of this dysfunction (105). These effects may be associated with increased platelet reactivity observed in subjects with MDD (106-108), as well as activation of inflammatory pathways in the disease (109). The association between depressive symptoms and increased platelet activity (106,110) involves the metabolism of catecholamines in platelets (106,108,111). Similarly, CVD has also been associated with increased platelet reactivity (112), inflammation and endothelial dysfunction (105), thus supporting a potential common etiological role for immune-inflammatory dysfunction in MDD and CVD. For instance, cytokine interleukin-10 levels predicted an adverse clinical outcome in chronic heart failure patients with depressive symptoms in a 1-year follow-up study (113). The increased activation of inflammatory cytokines and endothelial dysfunction described in the pathophysiology of MDD and CVD has been shown to involve concomitant dysfunctions in the hypothalamic-pituitary-adrenal (HPA) axis activity (109,113), which has also been shown to be regulated by MAO-A (as described below).

HPA activity. Dysfunctional HPA activity, including increased glucocorticoid activity, has been described in the pathophysiology of MDD (114). It has been proposed that enhanced cortisol agonistic effects during depressive episodes may contribute to an elevation in MAO-A levels (53). Severely depressed patients had significant increases in blood pressure, CSF and plasma NE, as well as elevated plasma cortisol (115). Notably, elevated platelet MAO activity associated with increased cortisol levels has been described in depression; platelet MAO activity has also been associated with severity of depressive symptoms (116). Notably, dexamethasone administration was shown to enhance MAO-A density in the brain by 300% (117), which supports a role for MAO-A in dysfunctional HPA axis activity described in MDD and CVD.

Similarly, dysregulation of the HPA axis and elevated cortisol levels may be a mediating factor between MDD and vulnerability to CVD. HPA axis dysregulation is also related to many CVD risk factors such as visceral obesity, hypercholesterolemia, hypertriglyceridemia, increased blood pressure, elevated heart rate and steroid-induced diabetes (118). In patients with CVD, prediction of cardiac events based on cortisol levels was directly influenced by oxidative stress parameters. Related to MAO-A activity, it was shown that NE stimulates the HPA via α- and β-adrenergic receptors (119). Urinary cortisol concentrations showed a positive correlation with urinary MAO-A activity (120).

5. Conclusions and perspectives

MDD increases the risk of cardiac mortality and morbidity in patients with CVD, and similarly CVD worsens the course and outcome of MDD, but little is known about the potential mechanisms involved in these effects. The pathophysiological findings of the association between depression and cardiac events are not consistent enough to be considered mediators, but clearly together modulate several aspects of these comorbid conditions. Reduced levels of MAO-A in the brain have been shown to induce a general increase in the resistance to the effects of environmental stressors (31), which has been critically implicated in the two conditions. Non-compliance to treatments may also represent an additional problem in this comorbidity. However, a more specific hypothesis is desirable.

Here, we describe an integrative model focusing on the effects of MAO-A in the comorbidity between MDD and CVD, based on a common mechanism. Enhanced sympathetic CNS activity and consequent increased breakdown of NE induced by excessive MAO-A activity is here proposed as a potential mechanism by which MDD increases cardiac morbidity. This dysregulation has been shown to increase production of ROS, also activating immuno-inflammatory responses and excessive glucocorticoids metabolism, which directly underlie the pathophysiology of MDD and CVD (Fig. 1). Since increased brain MAO-A appears to represent a trait marker in MDD, it is reasonable to suggest that this persistent increase may also contribute to similar changes in the periphery associated with the pathophysiology of CVD.

Further studies on the associations among family history, MAO-A polymorphisms and specific outcomes in these comorbid conditions are important. Future randomized

controlled trials using agents potentially able to treat MDD and CVD concomitantly and reverse common dysfunctional biological factors by inhibiting MAO-A activity (e.g., RIMAs) may be considered. It is also possible that a common genetic vulnerability associated with the MAO-A gene may be involved in comorbid MDD and CVD. In this context, MAO-A activity and the potential beneficial effects of MAO-A inhibitors related to oxidative stress and antioxidant status in the brain and heart deserve further studies.

Acknowledgements

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