23 Pharmacological Treatment and Prevention of Cardiovascular Diseases and Depression Comorbidity: Understanding Epidemiological, Clinical Trial Evidence, and the Biological Underpinnings

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Abstract

Depression and cardiovascular disease (CVD) are currently of major concern to public health and will be increasingly so in the future. These two disorders are closely interconnected both clinically and biologically. Understanding this interconnection is important to appreciating current and potential treatment and prevention platforms. There are a number of plausible biological models which may link depression and CVD together. Key models include a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis, chronic elevations in pro-inflammatory cytokines, increased sympathetic tone, platelet dysfunction leading to a pro-thrombotic state, as well as reductions in arterial vessel elasticity and endothelial dysfunction. The aim of this chapter is to review the epidemiological, clinical trial, and biological literature exploring the role of pharmacological treatment and prevention of depression and CVD. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), do appear useful in the treatment of comorbid depression and CVD, and they appear to play a role in the prevention of adverse cardiac events. The role of serotonin-noradrenaline reuptake inhibitors (SNRIs) is poorly understood and should be treated with caution. Anti-inflammatory therapies show promise in the treatment of depression; however, there is a paucity of clinical trial data on the role of anti-inflammatory therapies for the prevention of adverse cardiac events. An emerging body of research has now begun to explore the effect of pharmacological agents on inflammation, HPA axis dysfunction, increased sympathetic tone, and vascular and platelet dysfunction. This research should be continued to better understand the underlying mechanism of effect of pharmacological agents in comorbid depression and CVD.

23.1 Introduction

Depression and cardiovascular disease (CVD) are currently of major concern to public health and will be increasingly so in the future. An assessment of the World Health Organization's (WHO) Global Burden of Disease Study between 1990 and 2010 found the burden of ischemic heart disease (IHD) and depression increased substantially over this time (Murray et al. 2012). For IHD, the burden increased by 29 % to the number 1 ranked disorder; for depression, there was a 37 % increase in burden to number 11 (Murray et al. 2012). An earlier assessment of the Global Burden of Disease Study of 2004 predicted that by 2030, these disorders will be the two most common causes of disability-adjusted life years in the world (WHO 2008). Out of a sample of community-dwelling adults in the United States of America (aged >50 years) who had major depressive disorder (MDD), two-thirds had a diagnosis of heart disease, stroke, hypertension, and/or diabetes (Gonzalez and Tarraf 2013). In the future, depression and CVD will result in increased medical costs (Sullivan et al. 2002; Rutledge et al. 2009), increased health service utilization (Egede 2007), and lost productivity (Stewart et al. 2003). These two disorders are closely interconnected both clinically and biologically (Baune et al. 2012a, b). Understanding this interconnection is important to understanding current and potential treatment and prevention platforms.

The development of depression as a consequence of CVD has been explored extensively (Baune et al. 2012a, b). This may include depression as a consequence of an acute cardiac event (e.g., acute myocardial infarction (AMI)) or a chronic disease (e.g., congestive heart failure (CHF)) (Hare et al. 2014). After AMI, mild forms of depression have been found in up to two-thirds of hospitalized patients (Cay et al. 1972). The prevalence of depression in patients with CHF has been found to be dependent upon the severity of the functional class (Rutledge et al. 2006). In asymptomatic CHF, depression is found in around 10 % of patients and found in up to 40 % of patients with severe functional impairments (Rutledge et al. 2006).

The development of CVD as a consequence of depression has also been extensively explored (Baune et al. 2012a, b). Clinical and epidemiological studies suggest depression increases the risk of subsequent CVD by an average of 1.5-fold (Nicholson et al. 2006; Lippi et al. 2009; Grippo and Johnson 2002). Depression has been found to be an independent predictor of a worse outcome after an ischemic event (Barth et al. 2004; Meijer et al. 2011; Nicholson et al. 2006). Patients with comorbid coronary artery disease (CAD) and depression have a two- to threefold increased risk of future cardiac events compared to those only cardiac disease (Frasure-Smith and Lesperance 2010; Goldston and Baillie 2008; Van der Kooy et al. 2007; Rudisch and Nemeroff 2003). Depression in CHF patients is also an independent predictor of mortality and rehospitalization (Macchia et al. 2008).

There are a number of plausible biological models which may link depression and CVD together (Baune et al. 2012a, b). Key models include a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis, chronic elevations in pro-inflammatory

cytokines, increased sympathetic tone, platelet dysfunction leading to a pro-thrombotic state, as well as reductions in arterial vessel elasticity and endothelial dysfunction (Baune et al. 2012a, b). Studies investigating immune system functioning in individuals with depression have found that many of these individuals manifest chronically elevated inflammatory markers, particularly C-reactive protein (CRP), interleukin-6 (IL-6), IL-1β and tumor necrosis factor (TNF)-α (Dowlati et al. 2010; Eyre et al. 2014). This pro-inflammatory state is thought to be a key link in the comorbidity of depression and CVD (Paz-Filho et al. 2010; Lippi et al. 2009). Inflammation is implicated in the pathogenesis of CVD, particularly the development of atherosclerosis. Atherosclerosis may be accelerated through these inflammatory mediators via several mechanisms including chemoattraction of pro-inflammatory leukocytes to atherosclerotic lesions, the induction of endothelial activation and expression of adhesion molecules further increasing chemotactic signaling, and the stimulation of vascular endothelial growth factor (VEGF) production (Paz-Filho et al. 2010; Lippi et al. 2009). Inflammatory signaling cascades may also accelerate thrombus formation (Paz-Filho et al. 2010; Lippi et al. 2009). Disruptions of the HPA axis may be regulated by altered expression of pro-inflammatory cytokines, suggesting a complex bidirectional biological cross talk (Sasayama et al. 2011). The contribution of the HPA axis may be mediated, partly by the loss of glucocorticoid receptors (GRs) and their negative feedback function on inflammatory signaling, again leading to a further escalation in inflammation. Dysregulation of the HPA axis may also lead to sympathoadrenal hyperactivity, or increased sympathetic tone, via central pathways. Increased sympathetic tone is associated with processes implicated in the development of CVD, such as an increase in vasoconstrictive tone, heart rate, and platelet activation (Malpas 2010; Joynt et al. 2003). Finally, increased sympathetic tone may result in reduced heart rate variability (HRV), which is associated with risk of arrhythmias (Kemp et al. 2010). Endothelial dysfunction is a recognized risk factor for CVD; it is often observed in depressed patients without CVD (Shimokawa 1999; Rybakowski et al. 2006; Bonetti et al. 2003; Cooper et al. 2011). Depression is associated with reduced arterial elasticity, in addition to an increased expression of endothelial adhesion molecules and chemokines (Rajagopalan et al. 2001; Sherwood et al. 2005). Taken together, these factors may predispose patients to atherosclerosis, thrombosis, and vasospasm.

The exploration of treatment and prevention strategies for comorbid depression and CVD is highly important given the burden of these diseases and given complexity due to biological underpinnings, as well as significant patient safety factors in the post-CVD setting. Treatments may include psychotherapy, social therapy, somatic interventions (e.g., medications or electroconvulsive therapy), lifestyle therapies (e.g., physical activity, omega-3 polyunsaturated fatty acids), or a combination. Reviews of these modes of treatment can be found here (Ramamurthy et al. 2013; Honig et al. 2007). This review will focus on monoamine- and immune-modulatory psychopharmacological agents.

Monoamine-based antidepressants have a mixed evidence base supporting their use in CVD and depression. It appears that selective serotonin reuptake inhibitor

(SSRI) medications are safe as first-line therapies (Lichtman et al. 2009; Post-Myocardial Infarction Depression Clinical Practice Guideline 2009); however, studies in this area have limitations which will be discussed in this review. Tricyclic antidepressants (TCAs) are not recommended in CVD populations given their association with adverse cardiac events (Ramamurthy et al. 2013). Serotonin-noradrenaline reuptake inhibitors (SNRIs) appear to have a paucity of research supporting their use; hence caution is recommended (Ramamurthy et al. 2013).

Anti-inflammatory medications may be a useful tool in the treatment of depression and CVD given the role of pro-inflammatory cytokines linking these diseases (Eyre et al. 2015). Early data from meta-analyses suggests anti-inflammatories may indeed by useful in the treatment of depression without CVD (Kohler et al. 2014). However, this literature is heterogeneous and requires careful description and consideration (Eyre et al. 2015). There is some evidence supporting the use of anti-inflammatories in comorbid CVD and depression; this will be reviewed here.

To understand the role of the abovementioned pharmacological agents in depression and CVD, it is important to review epidemiological, clinical, and biological data. Particularly with respect to biological data, this is an emerging literature understanding the effects of antidepressants on inflammation, the HPA axis, sympathetic tone, and vascular biology. To date, we are not aware of a review which explores this topic systematically; hence this review provides novel perspectives on this. The aim of this chapter is to review the epidemiological, clinical trial, and biological literature exploring the role of pharmacological treatment and prevention of depression and CVD.

23.2 Antidepressant Pharmacotherapy to Treat Cardiovascular Disease and Depression

Treatment of depressive symptoms comorbid with CVD is crucial given depressive symptoms are associated with worse cardiovascular prognosis and lower quality of life. To this effect, treatments for depression need to be carefully studied given variously promising and concerning findings. Some antidepressants are useful to reduce depressive symptoms and show promise for improving cardiovascular outcomes, while others are not safe for use in CVD populations. Data from epidemiological and clinical trials is useful to understand efficacy and safety of antidepressants.

23.2.1 Epidemiological Evidence

There are a number of observational studies exploring the effects of antidepressants on comorbid depression and CVD. The hypothesized biological underpinnings for these findings are outlined further below in this paper. A study by Nabi et al. (2010) used a prospective cohort design to compare the significance of depression in CVD and cerebrovascular disease, as compared to subjects with no vascular disease. These subjects were taken from the Health and Social Support Prospective Cohort

Study and included a sample of 23,282 adults aged 20–54 years; they were followed for 7 years. Fatal and first nonfatal CVD and cerebrovascular disease events were documented by linkage to national hospital discharge and mortality registers. Results show the hazard ratio (HR) for CVD was 1.66 (95 % confidence interval (CI) 1.24–2.24) for participants with mild-to-severe depressive symptoms, i.e., those scoring ≥10 on the 21-item Beck Depression Inventory (BDI), and 2.04 (95 % CI 1.27–3.27) for those who filled antidepressant prescriptions (a suggested marker for clinically significant depression) compared with those without depression markers at study baseline. No subgroup analysis was conducted on type of antidepressant used. This suggests participants who filled antidepressant prescriptions have an increased risk of CVD; however, the results should be interpreted cautiously because medication use was utilized as a marker of depression severity.

A case-control study of subjects with IHD was used to determine whether antidepressants are a risk factor for IHD (Hippisley-Cox et al. 2001). In this study, 933 IHD subjects of any age (range from <50 to >90 years) were studied along with 5,516 controls. Odds ratios (ORs) for IHD were significantly raised for patients who had ever received a prescription for TCA after full adjustment 1.56 (95 % CI 1.18–2.05). Patients who had ever taken dothiepin had a significantly raised OR for IHD after full adjustment 1.67 (95 % CI 1.17–2.36). There was no significant increase in the OR for amitriptyline, lofepramine, and SSRIs in multivariate analysis. This suggests that patients who had ever taken dothiepin had significantly increased risk of IHD, with no other antidepressants significantly associated.

A study by Whang et al. (2009) explored the association between depression and sudden cardiac death (SCD) and cardiac events among individuals with baseline CVD in the Nurses' Health Study. Patient were ages 30–55 in 1976 when the study began, and they were followed over 8 years (1992–2000). Depression was measured by the Mental Health Index (MHI-5) and also antidepressant use. Primary end points included SCD, fatal CVD, and nonfatal MI. 63,469 women were involved in this analysis. In models from 1996 onward, clinical depression was most associated with SCD in multivariable models, HR 2.33 (95 % CI 1.47–3.70), and this was primarily due to the relationship between antidepressant use and SCD. From 2000 to 2004, similar HRs were found for the two categories of medications – SSRIs HR 5.07 (95 % CI 1.73–14.8) and other antidepressants HR 3.19 (95 % CI 0.92–11.00). This therefore suggests antidepressant use in both categories was associated with SCDs.

An observational study by Rieckmann et al. (2013) explored the association between SSRI and non-SSRI second-generation antidepressant use in a patient cohort with acute coronary syndrome (ACS) (within 1 week of hospitalization). They then explored the occurrence of cardiac events and mortality over a period of 42 months in participants aged around 60 years ± 15. This study was novel given current RCTs on this topic only monitor for adverse cardiac events for up to 6 months follow-up, which is considered a short time frame for such events. Four hundred thirty-two patients were grouped according to patients not on any antidepressant ($n = 354$), patients on SSRI only ($n = 78$), and patients on non-SSRI second-generation antidepressants only ($n = 20$). SSRI use carried an increased risk for

major adverse cardiovascular events (MACE) (i.e., hospitalization for nonfatal AMI, unstable angina, or urgent/emergency percutaneous or surgical coronary revascularization/mortality) compared to no antidepressant use hazard ratio [HR] (1.83; 95 % CI 1.09–3.06; $p=0.02$); non-SSRI second-generation antidepressant use did not HR, 0.86 (95 % CI 0.31–2.42; $p=0.78$). This study therefore suggests that SSRI use may be associated with longer-term risk for adverse prognosis in ACS patients; however, low numbers in this study should be taken into account.

Another prospective cohort study by Xiong et al. (2010) examined the association of perioperative coronary artery bypass grafting (CABG) bleeding risks and SSRI use prior to CABG. They explored 4,794 patients who underwent CABG surgery aged 54–72 years. Reoperation due to bleeding-related complications were not different between SSRI users OR 1.14 (95 % CI 0.52–2.47, $p=0.75$). The 30-day mortality (2.0 % in SSRI vs 2.1 % in control group; $p=0.92$) was similar. These data suggest there is no substantial increased risk of adverse events from SSRI use post-CABG surgery.

23.2.2 Clinical Trial Evidence

There are a number of clinical trials which explore the clinical and safety effects of antidepressants on patients with comorbid depression and CVD. These studies are outlined in Tables 23.1 and 23.2. Further, a number of meta-analyses have also been performed in this field. A meta-analysis by Mazza et al. (2010) explored SSRI vs control treatment in patients with recent ACS. Five RCTs (801 patients) were included, with an average age of 56.7 years. Subjects treated with SSRIs did not show a significant improvement in depression symptoms, after a median of 6 months, although there was a trend for a reduction. Subjects treated with SSRIs showed a significantly lower rate of rehospitalizations from all causes risk difference (RD) 14 % (95 % CI 5–23 %, $p=0.001$). Therapy with antidepressants was notably safe, with statistically similar rates of adverse events (i.e., MACE, death, AMI, and repeat revascularization). This suggests no effect of SSRIs on depressive symptoms, but improved or similar cardiac outcomes in patients with a recent ACS and depressive symptoms.

A Cochrane Collaboration meta-analysis (Baumeister et al. 2011) was performed to determine the effects of pharmacological and psychological interventions in CAD patients with comorbid depression. Primary outcomes were depression, mortality, and cardiac events. Secondary outcomes were healthcare costs and health-related quality of life (QoL). Eight RCTs were included with a total of 1,098 patients (see McFarlane et al. 2001; Lesperance et al. 2007; Freeman et al. 1986; Li et al. 2005; Liu and Zheng 1999; Glassman et al. 2002; Strik et al. 2000; Honig et al. 2007). The mean age of participants in these studies ranged from 54.1 to 63.6 years. It should be mentioned that the study by Freeman et al. (1986) utilized alprazolam; Li et al. utilized (2005) St. John's wort; Honig et al. (2007) utilized mirtazapine. The review provides evidence of a small beneficial effect of pharmacological interventions with SSRIs compared to placebo on depression outcomes (standardized mean difference

Table 23.1 Randomized controlled trials to evaluate the effects of antidepressant pharmacotherapy on depression in cardiovascular disease settings: depressive symptom outcomes

Ref	Aim	Population	Treatment period and groups	Outcome for depressive symptoms
Berkman et al. (2003)	To determine whether mortality and morbidity are reduced by treatment of depression and LPSS with CBT, supplemented with an SSRI	RCT; 2,481 MI patients (1,084 women, 1,397 men); minor or major depression (DSM-4); ESSI	CBT, initiated at a median of 17 days after the index MI for a median of 11 individual sessions throughout 6 months. Group therapy when feasible, with SSRIs for patients scoring higher than 24 on the HDRS or having a less than 50 % reduction in BDI scores after 5 weeks Usual care: 1,243, mean age 61 year (SD 12.5) Intervention: 1,238, mean age 61 year (SD 12.6)	Measures: HDRS; ESSI Results: improvement in psychosocial outcomes at 6 months favored treatment; mean (SD) change in HDRS score, −10.1 (7.8) in the depression and psychosocial intervention group vs −8.4 (7.7) in the depression and usual care group ($p<0.001$); mean (SD) change in ESSI score, 5.1 (5.9) in the LPSS and psychosocial intervention group vs 3.4 (6.0) in the LPSS and usual care group ($p<0.001$)
Glassman et al. (2002)	To evaluate the safety and efficacy of sertraline treatment of MDD	RCT; 369 patients with MDD DSM-4 (64 % male; mean age, 57.1 years; MI, 74 %; unstable angina, 26 %)	After a 2-week single-blind placebo run-in, patients were randomly assigned to receive sertraline ($n=186$) or placebo ($n=183$) for 24 weeks Placebo: mean age 57.6 years (SD 10.4) Sertraline: mean age 56.8 years (SD 11.1)	Measures: HAM-D scale and CGI-I Results: the CGI-I ($p=0.049$), but not the HAM-D ($p=0.14$), favored sertraline. The CGI-I responder rates for sertraline were significantly higher than for placebo in the total sample (67 % vs 53 %; $p=0.01$), in the group with at least 1 prior episode of depression (72 % vs 51 %; $p=0.003$), and in the more severe MDD group (78 % vs 45 %; $p=0.001$). In the latter 2 groups, both CGI-I and HAM-D measures were significantly better in those assigned to sertraline

Lesperance et al. (2007)	To explore efficacy of a SSRI (citalopram) and IPT in reducing depressive symptoms	RCT, 284 patients with CAD, all patients DSM-4 MDD of 4 weeks duration or longer, HAM-$D \geq 20$	12-week, parallel group; participants underwent 2 separate randomizations: (1) to receive 12 weekly sessions of IPT plus clinical management ($n=142$) or clinical management only ($n=142$) and (2) to receive 12 weeks of citalopram, 20–40 mg/day ($n=142$) or matching placebo ($n=142$)	Measures: 24-item HAM-D, BDI-II Results: citalopram was superior to placebo in reducing 12-week HAM-D scores (mean difference, 3.3 points; 96.7% CI, 0.80–5.85; $p=0.005$), with a small to medium effect size of 0.33. Mean HAM-D response (52.8% vs 40.1%; $p=0.03$) and remission rates (35.9% vs 22.5%; $p=0.01$) and the reduction in BDI-II scores (difference, 3.6 points; 98.3% CI, 0.58–6.64; $p=0.005$; effect size=0.33) also favored citalopram. There was no evidence of a benefit of IPT over clinical management, with the mean HAM-D difference favoring clinical management (−2.26 points; 96.7% CI, −4.78 to 0.27; $p=0.06$; effect size, 0.23). The difference on the BDI-II did not favor clinical management (1.13 points; 98.3% CI, −1.90 to 4.16; $p=0.37$; effect size=0.11)
Blumenthal et al. (2012)	To assess the efficacy of exercise and antidepressant medication in reducing depressive symptoms and improving cardiovascular biomarkers	101 outpatients with CHD and elevated depressive symptoms; DSM-4 for MDD	Randomized to 4 months of aerobic exercise (3 times/week), sertraline, or placebo Placebo: mean age 63.5 years (SD 11.4) Sertraline: mean age 63.4 years (SD 10.2) Exercise: mean age 64.7 years (SD 11.0)	Measures: HAM-D Results: after 16 weeks, all groups showed improvement on HAM-D scores. Participants in both aerobic exercise ($M=-7.5$ [95% CI=−9.8, −5.0]) and sertraline ($M=-6.1$ [95% CI=−8.4, −3.9]) achieved larger reductions in depressive symptoms compared to placebo ($M=-4.5$ [95% CI=−7.6, −1.5]; $p=0.034$); exercise and sertraline were equally effective in reducing depressive symptoms ($p=0.607$)

(continued)

Table 23.1 (continued)

Ref	Aim	Population	Treatment period and groups	Outcome for depressive symptoms
O'Connor et al. (2010)	To test the hypothesis that HF patients treated with sertraline will have lower depression scores and fewer cardiovascular events compared to placebo	RCT, sertraline vs placebo for 12 weeks, HF (LVEF ≤45 %, NYHA class IIIV), depression DSM-IV MDD	469 patients were randomized ($N=234$ sertraline, $N=235$ placebo) Placebo: mean age 61.4 years (SD 11.1) Sertraline: mean age 62.9 years (SD 10.5)	Measures: HDRS Results: the mean ± SE change from baseline to 12 weeks in the HDRS total score was −7.1 ± 0.5 (sertraline) and −6.8 ± 0.5 (placebo) ($p<0.001$ from baseline; $p=0.89$ between groups; mean change between groups −0.4, 95 % CI −1.7, 0.92)
Davidson et al. (2010)	To determine the acceptability and efficacy of enhanced depression treatment	A 3-month observation period to identify patients with ACS and persistent depressive symptoms was followed by a 6-month RCT	237 patients with ACS from 5 hospitals were enrolled, including 157 persistently depressed patients randomized to intervention (initial patient preference for problem-solving therapy and/or pharmacotherapy, then a stepped-care approach; 80 patients) or usual care (77 patients) and 80 nondepressed patients who underwent observational evaluation	Measures: patient satisfaction with depression care; BDI Results: the proportion of patients who were satisfied with their depression care was higher in the intervention group (54 % of 80) than in the usual care group (19 % of 77) (odds ratio, 5.4; 95 % CI, 2.2–12.9 [$p<0.001$]). The BDI score decreased significantly more (t (155) = 2.85 [$p=0.005$]) for intervention patients (change, −5.7; 95 % CI, −7.6 to −3.8; df = 155) than for usual care patients (change, −1.9; 95 % CI, −3.8 to −0.1; df = 155); the depression effect size was 0.59 of the standard deviation

Ye et al. (2014)	Examine cardiac events and mortality in the COPES trial through an additional 12 months of observational follow-up after the end of the 6-month treatment period	157 patients with a score of ≥10 on the BDI within 1 week of ACS hospitalization and again at 3-month follow-up. 80 enhanced treatment; 77 usual care Usual care: mean 61.1 (SD 10.6) Intervention group: mean 59.3 (SD 10.6)	Randomized to usual care or enhanced depression treatment involving stepped, patient preference-driven care with problem-solving therapy, pharmacotherapy, or both	Measures: BDI Results: at the beginning of the 12-month observational follow-up period, 58 of 77 patients (75 %) in the control group had a BDI score of ≥10, compared with 46 of 80 patients (58 %) in the intervention group ($p = 0.018$), suggesting that a substantial number of participants continued to have depressive symptoms

LPSS low perceived social support, *MI* myocardial infarction, *CBT* cognitive behavioral therapy, *SSRI* selective serotonin reuptake inhibitor, *BDI* Beck Depression Inventory, *CGI-I* Clinical Global Impression Improvement, *LVEF* left ventricular ejection fraction, *IPT* interpersonal psychotherapy, *HR* hazard ratio, *COPES* Coronary Psychosocial Evaluation Studies, *ACS*, acute coronary syndrome, *RCT* randomized controlled trial, *HF* heart failure, *NYHA* New York Heart Association, *DSM-IV* Diagnostic and Statistical Manual, *HRV* heart rate variability, *IPT* interpersonal therapy, *ECG* electrocardiogram, *VPC* ventricular premature complexes, *SD* standard deviation, *ESSI* Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Social Support Instrument (ESSI)

Table 23.2 Randomized controlled trials to evaluate the effects of antidepressant pharmacotherapy on depression in cardiovascular disease settings: cardiovascular morbidity and mortality outcomes

Ref	Aim	Population	Treatment period and groups	Outcome for cardiovascular morbidity	Outcome for mortality
Berkman et al. (2003)	To determine whether mortality and morbidity are reduced by treatment of depression and LPSS with CBT, supplemented with an SSRI	RCT; 2,481 MI patients (1,084 women, 1,397 men); minor or major depression (DSM-4); ESSI	CBT, initiated at a median of 17 days after the index MI for a median of 11 individual sessions throughout 6 months. Group therapy when feasible, with SSRIs for patients scoring higher than 24 on the HDRS or having a less than 50 % reduction in BDI scores after 5 weeks Usual care: 1,243; mean age 61 year (SD 12.5) Intervention: 1,238; mean age 61 year (SD 12.6)	Measures: recurrent MI Results: 4-year survival curves showed no significant difference between treatments in recurrence of MI Analyses of the time-dependent effect of pharmacologic therapy showed that antidepressant use was associated with a lower risk of reinfarction and/or mortality	After an average follow-up of 29 months, there was no significant difference in event-free survival between usual care (75.9 %) and psychosocial intervention (75.8 %). There were also no differences in survival between the psychosocial intervention and usual care arms in any of the 3 psychosocial risk groups (depression, LPSS, and depression and LPSS patients)

Glassman et al. (2002)	To evaluate the safety and efficacy of sertraline treatment of MDD	RCT; 369 patients with MDD DSM-4 (64 % male; mean age, 57.1 years; MI, 74 %; unstable angina, 26 %)	After a 2-week single-blind placebo run-in, patients were randomly assigned to receive sertraline ($n = 186$) or placebo ($n = 183$) for 24 weeks Placebo: mean age 57.6 years (SD 10.4) Sertraline: mean age 56.8 years (SD 11.1)	Measures: change from baseline in LVEF, surrogate cardiac measures, and cardiovascular adverse events Results: sertraline had no significant effect on mean (SD) LVEF (sertraline = baseline, 54 % [10 %]; week 16, 54 % [11 %]; placebo = baseline, 52 % [13 %]; week 16, 53% [13 %]), treatment-emergent increase in VPC runs (sertraline, 13.1 %; placebo, 12.9 %), QTc interval greater than 450 ms at end point (sertraline, 12 %; placebo, 13 %), or other cardiac measures. The incidence of severe cardiovascular adverse events was 14.5 % with sertraline and 22.4 % with placebo	Not detailed in paper

(continued)

Table 23.2 (continued)

Ref	Aim	Population	Treatment period and groups	Outcome for cardiovascular morbidity	Outcome for mortality
Lesperance et al. (2007)	To explore efficacy of a SSRI (citalopram) and IPT in reducing depressive symptoms	RCT, 284 patients with CAD, all patients DSM-4 MDD of 4 weeks duration or longer, HAM-$D \geq 20$	12-week, parallel group; participants underwent two separate randomizations: (1) to receive 12 weekly sessions of IPT plus clinical management ($n = 142$) or clinical management only ($n = 142$) and (2) to receive 12 weeks of citalopram, 20–40 mg/day ($n = 142$) or matching placebo ($n = 142$)	Measures: ECG, blood pressure Results: there were no differences between citalopram and placebo in any blood pressure or electrocardiographic measures, including QTc intervals. However, patients receiving IPT experienced a slight increase in systolic blood pressure at 12 weeks in comparison with a slight decrease among patients receiving clinical management alone	Not detailed in paper
Blumenthal et al. (2012)	To assess the efficacy of exercise and antidepressant medication in reducing depressive symptoms and improving cardiovascular biomarkers	101 outpatients with CHD and elevated depressive symptoms; DSM-4 for MDD	Randomized to 4 months of aerobic exercise (3 times/week), sertraline, or placebo Placebo: mean age 63.5 years (SD 11.4) Sertraline: mean age 63.4 years (SD 10.2) Exercise: mean age 64.7 years (SD 11.0)	Measures: HRV, endothelial function, baroreflex sensitivity, inflammation, platelet function Results: exercise and medication tended to result in greater improvements in HRV compared to placebo ($p = 0.052$); exercise tended to result in greater improvements in HRV compared to sertraline ($p = 0.093$)	Not detailed in paper

O'Connor et al. (2010)	To test the hypothesis that HF patients treated with sertraline will have lower depression scores and fewer cardiovascular events compared to placebo	RCT; sertraline vs placebo for 12 weeks; HF (LVEF ≤45 %, NYHA class II–IV); depression DSM-IV MDD	469 patients were randomized ($N=234$ sertraline, $N=235$ placebo) Placebo: mean age 61.4 years (SD 11.1) Sertraline: mean age 62.9 years (SD 10.5)	Measures: composite cardiovascular status; cardiovascular events and survival during the short-term treatment phase and long-term follow-up were also assessed Results: the proportion whose composite cardiovascular score worsened, improved, or was unchanged was 29.9 %, 40.6 %, and 29.5 % in the sertraline group and 31.1 %, 43.8 %, and 25.1 % in the placebo group ($p=0.78$)	Measures: serious adverse events Results: serious adverse events were not statistically different between the groups
Davidson et al. (2010)	To determine the acceptability and efficacy of enhanced depression treatment	A 3-month observation period to identify patients with ACS and persistent depressive symptoms was followed by a 6-month RCT	237 patients with ACS from 5 hospitals were enrolled, including 157 persistently depressed patients randomized to intervention (initial patient preference for problem-solving therapy and/or pharmacotherapy then a stepped-care approach; 80 patients) or usual care (77 patients) and 80 nondepressed patients who underwent observational evaluation	Measures: see mortality column	Measures: death and major adverse cardiac events Results: 3 intervention patients and 10 usual care patients had experienced major adverse cardiac events (4 % and 13 %, respectively; $p=0.047$), as well as 5 nondepressed patients (6 %) (for the intervention vs nondepressed cohort, $p=0.49$)

(continued)

Table 23.2 (continued)

Ref	Aim	Population	Treatment period and groups	Outcome for cardiovascular morbidity	Outcome for mortality
Ye et al. (2014)	Examine cardiac events and mortality in the COPES trial through an additional 12 months of observational follow-up after the end of the 6-month treatment period	157 patients with a score of ≥10 on the BDI within 1 week of ACS hospitalization and again at 3-month follow-up. Eighty enhanced treatment; 77 usual care Usual care: mean 61.1 (SD 10.6) Intervention group: mean 59.3 (SD 10.6)	Randomized to usual care or enhanced depression treatment involving stepped, patient preference-driven care with problem-solving therapy, pharmacotherapy, or both	Measures: major adverse cardiac events, defined as nonfatal MI or hospitalization for unstable angina Results: a significant time-by-treatment group interaction during extended follow-up ($p=0.008$). Specifically, during the 6-month treatment period, death or hospitalization for MI/unstable angina occurred in 3 participants (4%) in the treatment group compared with 11 participants (14%) in the usual care group (HR, 0.25; 95% confidence interval, 0.07–0.90; $p=0.03$). In contrast, during 12 months of additional observational follow-up, 11 participants (14%) in the treatment group experienced the composite outcome of death or hospitalization for MI/unstable angina compared with 3 participants (4%) in the usual care group (HR, 2.91; 95% confidence interval, 0.80–10.56; $p=0.10$)	Not detailed in paper

(SMD) of short-term depression change scores, –0.24 (–0.38–0.09), OR of short-term depression remission: 1.80 (95 % CI 1.18, 2.74)). No beneficial effects regarding mortality, cardiac events, and QoL were found. Hospitalization rates (OR of three trials, 0.58 [95 % CI 0.39, 0.85]) and emergency room visits (OR of one trial, 0.58 [95 % CI 0.34, 1.00]) were reduced in trials of pharmacological interventions compared to placebo. The authors suggest the research agenda in this field may need to explore patients based on their specific depression subtype and severity, and only few studies were available to explore outcomes for QoL, mortality, and cardiac events.

A latest quantitative analysis of this field, from Pizzi et al. (2011), was conducted to evaluate the effects of SSRIs versus placebo or no antidepressants in patients with CVD and depression. Primary outcomes were readmission for CVD (including AMI, unstable angina, and stroke) and all-cause mortality; the secondary outcome was severity of depression symptoms. Seven studies on six RCTs involving 2,461 participants were included, with a mean age similar in all trials and approximately 58 years. The four properly randomized trials constituted 734 patients (see Glassman et al. 2002; Lesperance et al. 2007; Strik et al. 2000; McFarlane et al. 2001; and Tables 23.1 and 23.2), while two other studies were categorized as "observational," i.e., RCTs with high risk of bias in randomization process – 1,727 subjects (see Taylor et al. 2005; Mohapatra et al. 2005; and Tables 23.1 and 23.2). When only the correctly randomized trials were taken into account, patients on SSRIs showed no significant differences in mortality RR 0.39 (95 % CI 0.08–2.01) or CVD readmission rates RR 0.74 (95 % CI 0.44–1.23) compared to controls. A significantly greater improvement in depression symptoms was always apparent in patients on SSRIs with all selected indicators. This study suggests SSRIs do decrease depressive symptoms and may improve CVD prognosis. This analysis suggests that a number of these trials were not adequately powered (see Glassman et al. 2002; Strik et al. 2000; Lesperance et al. 2007; Mohapatra et al. 2005; Hippisley-Cox et al. 2001). It was not possible to stratify these analyses to explore associations between various clinical outcomes and different types and doses of SSRIs.

23.2.3 Summary and Recommendation

When considering data from this field, consensus statements suggest SSRIs are recommended as first-line antidepressant treatments for depressed patients with CVD (Lichtman et al. 2009; Post-Myocardial Infarction Depression Clinical Practice Guideline 2009). It is clear given the data from epidemiological and clinical trials is conflicting when considering efficacy and safety. However, when high quality meta-analyses of RCTs are taken into account, SSRIs appear effective as a first-line antidepressant therapy for comorbid CAD and depression. The evidence of effects on mortality and morbidity is conflicting and suggests no difference to placebo. It is clear from a clinical perspective that careful follow-up is needed in the "real world" setting. Studies with longer follow-up are also required as the majority of current RCTs only follow subjects for 6 months. It is clear that TCAs do not appear safe for use in this population. There is a paucity of data on the use of SNRIs; hence caution is suggested with these

medications (Ramamurthy et al. 2013). Larger studies are required to understand cardiac outcomes. A systematic review by Ramamurthy et al. (2013) highlights that an estimated 4,000 subjects are needed in RCTs to detect a 20 % risk reduction in medical events from CAD. Based on this, no studies to date have been adequately powered to fully explore these changes. Finally, it is unclear in the literature how aging is associated with the efficacy and safety of antidepressants in comorbid CVD and depression.

23.3 Antidepressant Pharmacotherapy to Treat Depression and Congestive Heart Failure

23.3.1 Epidemiological Evidence

We are aware of only one epidemiological study exploring the associations between antidepressant use and outcomes in patients with CHF. In this study (Sherwood et al. 2007), 204 subjects with a diagnosis of CHF (left ventricular ejection fraction (LVEF) ≤40 %) underwent baseline assessments with BDI. Depression and CHF were followed for 3 years using the BDI and B-type natriuretic peptide (BNP). Primary end points included death and CVD-related hospitalizations. The mean age at baseline was 56.8 years with a range of 27–88 years. After full adjustment, antidepressant medication use (various types) was associated with increased likelihood of death or cardiovascular hospitalization HR 1.75 (95 % CI 1.14–2.68, $p=0.01$). The authors suggest patients with CHF requiring antidepressant medication should be monitored closely for adverse events. Replication of this study is clearly required.

23.3.2 Clinical Trial Evidence

We are again only aware of one clinical trial exploring the effects of antidepressants on patients with comorbid depression and CHF (see Tables 23.1 and 23.2). In an RCT by O'Connor et al. (2010), the effects of sertraline vs placebo were assessed on depression scores and cardiovascular events in patients with comorbid depression and CHF. Eligible patients were age ≥45 years with HF (LVEF ≤45 %, New York Heart Association class II–IV) and clinical depression (DSM-IV criteria for current major depressive disorder). Primary end points were change in depression severity (Hamilton Depression Rating Scale, HDRS) and composite cardiovascular status at 12 weeks. Four hundred sixty-nine patients were randomized – $N=234$ for sertraline and $N=235$ for placebo. The change from baseline to 12 weeks in the HDRS total score was mean -7.1 ± 0.5 (sertraline) and -6.8 ± 0.5 (placebo) ($p<0.001$ from baseline, $p=0.89$ between groups, mean change between groups 0.92). The proportion whose composite cardiovascular score worsened, improved, or was unchanged was 29.9 %, 40.6 %, and 29.5 % in the sertraline group and 31.1 %, 43.8 %, and 25.1 % in the placebo group ($p=0.78$). This suggests sertraline was safe in CHF patients; however, there was no difference between sertraline and placebo in antidepressant effects.

23.3.3 Summary and Recommendation

There is a paucity of evidence in the treatment of depression and CHF; hence this is an important area for further investigation. SSRIs appear to be safe and had a minimal effect on depressive symptoms.

23.4 Antidepressant Pharmacotherapy to Prevent Cardiovascular Disease in Depressed Patients

23.4.1 Epidemiological Evidence

We are aware of one meta-analysis (Oh et al. 2014) exploring the association between antidepressant use and the risk of CVD in subjects free of CVD. In this study, 16 observational studies were included, 6 population-based case-control studies, 1 nested case-control study, 1 retrospective cohort study, and 8 prospective cohort studies. Participants were from a wide age range. Antidepressants were divided into SSRIs and TCAs. CVD outcomes were defined as fatal and nonfatal AMI and other IHD. There was no association found between SSRIs use and the risk of CVD overall OR 0.93 (95 % CI 0.65–1.33). The use of TCAs was associated with an increased risk of CVD overall OR 1.51 (95 % CI 1.07–2.12), but it was observed only in case-control studies OR 1.56 (95 % CI 1.24–1.96) and low-quality studies OR 1.49 (95 % CI 1.20–1.85) in the subgroup meta-analysis. This suggests no association between SSRI use and CVD risk; however, TCAs showed an increased risk. The rationale for this will be outlined below.

23.4.2 Clinical Trial Evidence

There are currently no published RCTs addressing antidepressant use and its effect on the development of CVD in patients without preexisting CVD.

23.5 Anti-inflammatory Pharmacotherapy to Treat Comorbid CVD and Depression

23.5.1 Background Information

As mentioned previously, inflammatory processes are suggested to play an important part in the development of depression, and it is believed that inflammation may be a promising target in the treatment and prevention of depression. Given this clinical and biological relationship between inflammation and depression, both selective cyclooxygenase (COX)-2 and nonselective COX inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated as possible adjuncts in the treatment of depression. Our group critically and systematically reviewed the literature to determine whether selective COX-2 and nonselective COX inhibitor NSAIDs as

adjunctives and monotherapies affect depressive symptoms (Eyre et al. 2015). In our analysis on adjunctive and monotherapy studies, we included six RCTs exploring the efficacy of selective COX-2 inhibitor NSAIDs on depressive symptoms with a total of 2,706 subjects. Four of the RCTs showed a significant effect of NSAIDs; two demonstrated no effect. There were a total of five studies exploring the efficacy of nonselective COX inhibitor NSAIDs on depressive symptoms with a total of 7,978 subjects. There was one RCT, three cohort studies, and one open-label pilot study. The RCT failed to show a significant result. One of the retrospective cohort studies showed a positive result, with the other two showing no effect. We concluded the efficacy of NSAIDs on depressive symptoms appears negligible; however, firm conclusions are difficult given the inconsistent findings and substantial methodological heterogeneity. Heterogeneity was derived from a variety of factors, i.e., age range, sex, presence of antidepressant use, method of depression measure, severity of depressive symptoms, duration, and study design (RCT vs cohort). A meta-analysis (Na et al. 2014) of RCTs suggests that celecoxib, a selective COX-2 inhibitor NSAID, has a therapeutic effect when used adjunctively with other antidepressants. This study utilized four RCT studies with a total of 150 patients. The patients receiving adjunctive celecoxib had significantly higher mean changes in the HDRS scores between baseline and end point measurements compared with those receiving placebo (weighted mean difference = 3.26). The adjunctive celecoxib group also showed better remission OR = 6.58 and response rates OR = 6.49 than the placebo group. Yet another meta-analysis by Kohler et al. (2014) explored the antidepressant effects of all anti-inflammatory interventions. Ten publications reporting on 14 trials (6,262 participants) were included; ten trials evaluated the use of NSAIDs (n = 4,258; four as adjunct treatment and six as monotherapy all including celecoxib) and four investigated cytokine inhibitors (n = 2,004; all studies as monotherapy). These were a mix of adjunctive (to antidepressants) and monotherapy studies. The pooled effect estimate suggested that anti-inflammatory treatment reduced depressive symptoms SMD −0.34 compared with placebo. This effect was observed in studies including patients with depression SMD −0.54 and depressive symptoms SMD −0.27. A subanalysis of celecoxib only showed a trend toward superiority to placebo (SMD −0.29). When celecoxib monotherapy studies where only examined, results were borderline significant (SMD −0.13); celecoxib adjunct studies showed significant improvement (SMD −0.82). Among the six studies reporting on adverse effects, there was no evidence of CVD events after 6 weeks of anti-inflammatory treatment compared with placebo.

Taken together, these findings suggest anti-inflammatory pharmacological agents should be studied more in the treatment of depression and CVD both as adjunctive treatment as well as monotherapy. At this stage, adjunctive celecoxib treatments appear to be most effective for the treatment of depression.

23.5.2 Epidemiological Evidence

We are only aware of one published study exploring the effects of anti-inflammatories on comorbid depression and CVD. In this observational study (Rieckmann et al. 2011),

data from 168 ACS hospitalized patients were assessed along with adherence to aspirin medication. Adherence to aspirin was measured over 90 days, and rates of antidepressant use were not recorded, although present. The outcome was the 1-year first occurrence of a MACE or all-cause mortality. Controlling for age, sex, and site, baseline depressive symptoms were significantly correlated with poorer 7-day, 1-month, and 3-month aspirin adherence (all $p<0.02$). After 1 year, there had been 14 MACE/all-cause mortality events (8%). Adjusting for age, sex, and site, poorer 7-day (HR 1.76) and 1-month aspirin adherence (HR 1.75) as well as baseline depressive symptoms (HR 1.53) were each individually associated with 1-year MACE/all-cause mortality. These findings suggest poorer aspirin adherence may account for a proportion of the excess prognostic risk associated with depressive symptoms after ACS. There is thus rational for a clinical trial in this area.

23.6 Understanding the Neurobiological Mechanisms Subserving the Effects of Antidepressants in Depression and Cardiovascular Disease

There are a number of neurobiological mechanisms potentially subserving the efficacy and safety of antidepressants in depression and CVD. These mechanisms include inflammation, HPA axis dysfunction, increased sympathetic tone, vascular dysfunction, and cardiac conduction. In the below sections, we review each of these mechanisms and explore the effect of antidepressants on them. We have aimed to distinguish the neurobiological effects of various classes of antidepressants where possible. A diagrammatic overview of this section is also provided in Fig. 23.1.

23.6.1 Inflammation

The most recent evidence from reviews and meta-analyses suggests that antidepressants may exert effects on the immune system. A meta-analysis of 22 studies by Hannestad et al. (2011) explored the effect of antidepressants on serum pro-inflammatory cytokines, TNFα, IL-1β, and IL-6, in 603 depressed subjects. This is the latest study to quantitatively explore the immune-modulatory effects of antidepressants. A stratified subgroup analysis in this meta-analysis by class of antidepressants indicated that serotonin reuptake inhibitors (SSRI) may reduce levels of IL-6 and TNFα, whereas other types of antidepressants – while efficacious for depressive symptoms – did not appear to reduce cytokine levels and showed only limited evidence in a few studies only. These data suggest that SSRIs with their prominent serotonergic functions may be more anti-inflammatory than other agents. Beyond this meta-analysis, it has been suggested that while noradrenaline reuptake inhibitor antidepressants suppress Th1-type cytokines (e.g., IFN-γ, IL-2, and TNF-α) and shift the balance toward humoral immunity, serotonin reuptake inhibitors reduce the production of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) and shift the balance toward cellular immune response (Uher et al. 2014; Martino et al.

2012). These findings suggest that antidepressants do appear to be anti-inflammatory, and hence this may be one mechanism through which they reduce depressive symptoms and CVD-related health issues. However, the abovementioned data raise the possibility of differential mechanistic effects of various antidepressant classes on immune function. We caution conclusions regarding which antidepressant possesses the greater anti-inflammatory effect given methodological heterogeneity among studies and a small number of comparative studies.

23.6.2 HPA Axis

One of the most consistent biological findings in depression is a hyperactivity of the HPA axis, and there is a literature exploring the effects of antidepressants on this (Pariante and Lightman 2008). Data from both preclinical and clinical studies assists in understanding the effects of antidepressants on the HPA axis. A study by Cattaneo et al. (2013) tested leukocyte mRNA expression levels of genes in healthy controls ($n=34$) and depressed patients ($n=74$), both before and after 8 weeks of treatment with escitalopram or nortriptyline. This was conducted as part of the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. Genes were explored common to both drugs. Nonresponders had higher baseline mRNA levels of IL-1β (+33 %), macrophage inhibitor factor (MIF) (+48 %), and TNF-α (+39 %). This suggests a pro-inflammatory state is associated with nonresponse. Antidepressants reduced the levels of IL-1β (−6 %) and MIF (−24 %) and increased the levels of GR (+5 %) and p11 (+8 %); however, these changes were not associated with response. Responders had a reduction in the levels of the GR-associated gene, *FKBP-5*. This suggests depression is characterized by the coexistence of higher *FKBP-5* and lower *GR*, possibly leading to GR resistance. Furthermore, successful antidepressant treatment requires normalization of GR function. In another human study, Carvalho et al. (2010) explored the effects of antidepressants (clomipramine, amitriptyline, sertraline, paroxetine, and venlafaxine) on GR function. GR function was assessed in peripheral blood cells from 33 health volunteers. GR function was measured by glucocorticoid-mediated inhibition of lipopolysaccharide (LPS)-stimulated interleukin-6 (IL-6) levels. LPS is a potent immune system activator. Compared to vehicle-treated cells, all antidepressants inhibited dexamethasone (DEX, 10–100 nM) inhibition of LPS-stimulated IL-6 levels (p values ranging from 0.007 to 0.1). The GR antagonist, RU-486, inhibited the effect of antidepressants on GR function. Research in neuronal stem cells has illustrated that antidepressants directly increase the function of the GR (Anacker et al. 2011). This was found to occur via a GR-dependent mechanism, i.e., the expression of *p11* (Anacker et al. 2011). The effect on p11 is an action that is required for the effects of antidepressants on neurogenesis (Anacker et al. 2011). These studies highlight the effects of antidepressants on the HPA axis and their role in correcting HPA axis dysfunction, which is likely associated with reducing inflammatory processes.

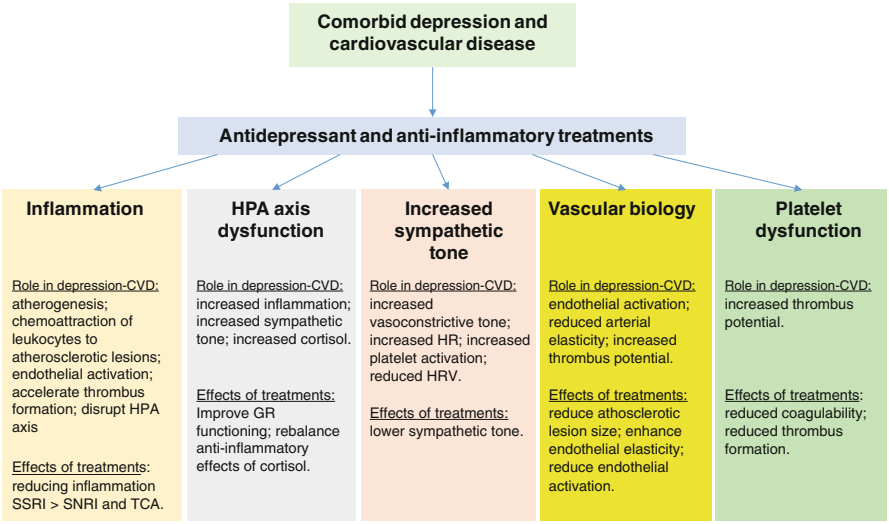

Fig. 23.1 Neurobiological mechanisms subserving the effects of antidepressants and anti-inflammatories on the treatment of depression and cardiovascular disease

23.6.3 Sympathetic Tone

HRV is a measure of sympathetic tone and is an important marker given very low-frequency (VLF) HRV may predict mortality in patients with comorbid depression and CVD (Carney et al. 2005). A prospective cohort study, the Heart and Soul Study (Zimmermann-Viehoff et al. 2014), was utilized to explore associations between antidepressant use (SSRI or TCA) and mortality in patients with CVD and HRV. Nine hundred fifty-six patients with CVD were followed for a mean duration of 7.2 years. Of 956 patients, 44 (4.6 %) used TCAs, 89 (9.3 %) used SSRIs, and 823 (86.1 %) did not use antidepressants. At baseline, TCA users exhibited lower HRV compared with SSRI users and antidepressant nonusers. At the end of the observational period, 52.3 % of the TCA users had died compared with 38.2 % in the SSRI group and 37.3 % in the control group. The adjusted HR for TCA use compared with nonuse was 1.74 ($p=0.01$). Adjustment for measures of autonomic function rendered nonsignificant the association between TCA use and mortality. SSRI use was not associated with mortality. This suggests the associations between TCA use and mortality may be partly mediated by effects on autonomic function. A recent pilot study (Jain et al. 2014) examined the associations between resting baseline HRV and depression treatment outcomes. In this study, investigators retrospectively tested several parameters of HRV in an MDD treatment study with escitalopram ($n=26$) as well as Iyengar yoga ($n=16$). Lower relative power of very low-frequency (VLF) HRV at baseline predicted improvement in depressive symptoms when adjusted for age and gender ($p<0.05$ for both treatments). This suggests VLF HRV may be a useful predictor of treatment outcome with antidepressants in

depression; however, the underlying biology for this is unclear. A recent RCT by Blumenthal et al. (2012) explored the effects of aerobic exercise and sertraline in reducing depressive symptoms and certain CV biomarkers in depressed patients with CVD. One hundred participants were involved in this study and were offered 4 months of aerobic exercise, sertraline, or placebo. After 16 weeks, both the aerobic exercise group and sertraline group showed a larger reduction than placebo for depressive symptoms. Exercise and sertraline were equivalent in their antidepressant effects. Exercise and medication showed a trend toward a greater improvement in HRV than placebo. This suggests antidepressants may improve cardiovascular biomarkers. In summary, these studies show antidepressants may improve HRV; however, there are few studies in this area.

23.6.4 Vascular Biology

A number of studies have explored the effects of antidepressants of markers of vascular biology in depression. A recent case-control study (Paranthaman et al. 2012) explored the relationship between endothelial function, atherosclerosis, and treatment response to antidepressant monotherapy (various types). The study compared 25 patients with late-life depression to 21 nondepressed subjects. Vascular measures included a marker of atherosclerosis (carotid intima thickness (IMT)) and endothelial function (biopsied small artery dilatation/reactivity to acetylcholine). There was a significant group difference (responders versus nonresponders versus controls) on both IMT and endothelial function ($p<0.05$ for both). There was a gradient across groups, with control subjects having best vascular structure or function, nonresponders having the worst, and responders at an intermediate level. These findings suggest that vascular dysfunction and pathology are linked to lesser antidepressant response.

A subgroup analysis of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) study (Serebruany et al. 2003) was used to understand the effects of sertraline on the release of platelet and endothelial biomarkers in depressed subjects with ACS. In this analysis 55 subjects were randomly assigned to sertraline ($n=23$) or placebo ($n=32$). Anticoagulants, aspirin, and clopidogrel were permitted. Twenty-six serial plasma samples collected at week 6 ($N=12$) and week 16 ($N=14$) were analyzed. Platelet factor 4 (PF4), β-thromboglobulin (β-TG), platelet/endothelial cell adhesion molecule 1 (PECAM-1), P-selectin, thromboxane B_2 (TxB_2), prostacyclin (6-keto-PGF1α), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin were measured by enzyme-linked immunosorbent assay. Negative correlations were found for the plasma levels of sertraline and *N*-desmethylsertraline with PF4, β-TG, PECAM-1, P-selectin, and TxB_2. These findings allude to sertraline reducing platelet and endothelium activation.

A study by van Zyl et al. (2009) utilized an RCT framework (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE)) to explore whether treatment of depressed CAD patients with citalopram altered platelet and endothelial biomarkers. The effect of citalopram was explored on P-selectin, β-TG, soluble intercellular CAM-1 (sICAM-1), and total

nitric oxide (tNO). Plasma samples were obtained at baseline and week 12 from subjects randomized to citalopram ($n=36$) or placebo ($n=21$). Anticoagulants, aspirin, and clopidogrel were permitted. Treatment with citalopram was associated with greater increase in tNO over 12 weeks compared to placebo ($p=0.005$). There were no differences for the other biomarkers. Improved endothelial function may be implied by the increased NO production in this study; however, this is not clear. Some studies show SSRIs inhibit NO (Finkel et al. 1996), and others suggest SSRIs increased NO and its metabolites (Lara et al. 2003; Chrapko et al. 2006). The differing results in this study as compared to the abovementioned SADHART subgroup analysis may be due to differing stages of CVD or the different effects of sertraline vs citalopram.

23.6.5 Platelet Dysfunction

As mentioned previously, platelet dysfunction is a potential biological mechanism connecting depression and CVD. Platelets possess receptors for serotonin (5-HT), such as 5-HT2A and 5-HT3, and also a 5-HT transporter (SERT) in their membranes (Stratz et al. 2008). 5-HT is stored in the dense granules within platelets and released during stimulation. Preclinical studies have demonstrated that 5-HT potentiates procoagulant responses of platelets and enhances the thrombogenesis on damaged vascular surfaces (Galan et al. 2009; Lopez-Vilchez et al. 2009).

An interesting exploration of the role of antidepressants in platelet function comes from an analysis of cerebral microbleeds (Aarts et al. 2014). Within the population-based Rotterdam Study, information on antidepressant use was obtained from continuously monitored pharmacy records, and brain MRIs were available in 4,945 participants between 2005 and 2011. Antidepressants were categorized based on affinity for the serotonin transporter: high, intermediate, or low. Antidepressant use with strong serotonin reuptake inhibition was not associated with microbleed presence (OR 1.03), compared with nonuse, irrespective of microbleed location in the brain. Exclusion of antithrombotic users or persons with cortical infarcts did not change these results. Furthermore, serotonergic antidepressant use was not related to ischemic vascular brain damage. This data suggests serotonin-active antidepressants do not relate to the presence of cerebral microbleeds.

A recent clinical study (Lopez-Vilchez et al. 2014) investigated the modulation of thrombogenesis by treatment with an SSRI. Modifications in a series of biomarkers of platelet and coagulation activation were evaluated in the blood from 19 patients with an MDD at the time of diagnosis, and at 8 and 24 weeks of treatment with escitalopram, 20 healthy subjects were used as controls. Response of blood aliquots recirculated through a thrombogenic surface was assessed as a thrombosis model. In comparison with controls, platelets from depression patients showed elevated clot volumes, augmented expression of GPIb, fibrinogen, factor V, and phospholipids. Clot firmness and procoagulant activity of platelet-associated tissue factor were also significantly elevated. Studies with circulating blood revealed increased fibrin formation in early diagnosed patients. After 24 weeks of treatment

with escitalopram, the majority of the alterations observed were normalized, except for biomarkers of viscoelasticity and clot formation which were unaffected. This data demonstrates the pro-thrombotic state seen in depression and the effect of SSRIs in altering certain biomarkers, although not others.

23.6.6 Cardiac Conduction

Cardiac conduction is clearly crucial in understanding the effects of antidepressants on patients with depression and CVD. The effect of antidepressants on cardiac conduction systems is likely strongly related to cardiac-related adverse events.

23.6.6.1 Selective Serotonin Reuptake Inhibitors

SSRIs have been associated with very infrequent cardiac side effects, such as bradycardia and heart block (86 reported cases of the first 2.5 million taking fluoxetine (Goldberg 1998)). The Food and Drug Administration in the United States has advised that citalopram not exceed 40 mg daily to prevent prolonged QTc and associated arrhythmias. Some authors suggest benefit from serial electrocardiograms and cardiac/internal medicine consultation when adding SSRIs to patients with pre-existing arrhythmias, particularly bradycardia/atrioventricular block (Ramamurthy et al. 2013).

23.6.6.2 Serotonin Noradrenaline Reuptake Inhibitors

As mentioned previously, caution is advised with the use of SNRIs in depression and CVD. The hypothetical concern is with SNRIs increase sympathetic tone through noradrenergic action. High sympathetic tone is associated with atherogenesis (Julius 1993), cardiac remodeling post-AMI (Sabbah 2004), and arrhythmias (Hjalmarson 1997).

23.6.6.3 Tricyclic Antidepressants

Data from the Cardiac Arrhythmia Suppression Trial (CAST) (Glassman et al. 1993) published in 1993 in which post-MI patients were treated with various classes of pharmacological agents was revealing in regard to the safety of TCAs. This study showed Class 1 antiarrhythmics, where TCAs are categorized, had increased mortality.

Conclusions

The tremendous burden of depression, CVD, and their comorbid status makes the need for understanding current and developing new treatments and preventive strategies highly important. When we consider antidepressant and anti-inflammatory therapies from epidemiological and clinical trial perspectives, there are a number of interesting findings, as well as areas for further research. When considering clinical efficacy, SSRIs appear to be effective as first-line antidepressants. There is a paucity of data for SNRIs, and TCAs are not recommended. Celecoxib treatment may be useful as an adjunctive treatment, with

other anti-inflammatories requiring further investigation. The effect of SSRIs on mortality and morbidity appears minimal, with a mixture of results suggesting no different to placebo and improved results to placebo. There are a number of biological systems which are implicated in the bidirectional relationship between depression and CVD, including inflammation, HPA axis dysfunction, increased sympathetic tone, and vascular and platelet dysfunction. An emerging body of research has now begun to explore the effect of pharmacological agents on these systems. More research is required to understand the effects of various drug classes on these mechanisms. In the future, we have a number of recommendations to advance this field. Larger and longer duration RCTs are required to determine the effect of various types of antidepressants on long-term CVD outcomes. Further, understanding the effects of antidepressant treatments on various types of depression (e.g., melancholic, non-melancholic, and atypical) would be helpful to understand effects on CVD outcomes. Exploration of the treatment of depression and comorbid CHF is also an area in need of further examination.

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