

Treatment of anxiety and depressive disorders in patients with cardiovascular disease

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What role do selective serotonin reuptake inhibitors have in treating psychiatric morbidity in patients with cardiovascular disease? This review discusses the safety and efficacy of various antidepressants in this group of patients and their potential for improving cardiovascular outcomes

Anxiety and depressive disorders are common in the general population and are particularly prevalent in patients with cardiovascular disease (box 1).^{1-3 w1-w3} We reviewed evidence for a biological explanation for this association and for drug treatment and psychotherapy for psychiatric morbidity in patients with cardiovascular disease.

Sources and selection criteria

We systematically searched Medline (1966 to August 2003 through Ovid) and Embase (1980 to October 2002) for all relevant English language articles. Firstly, we entered terms and text words including myocardial infarction, angina, hypertension, stroke, cerebrovascular, and poststroke. Secondly, we used the terms and text words “SSRIs”, “serotonin reuptake inhibitors”, and individual drug names. The searches were combined and relevant articles retrieved. The reference lists were searched for other potentially relevant articles.

Cardiovascular disease and psychiatric morbidity

Much evidence links depression with coronary artery disease and hypertension; 16% of patients assessed seven days after myocardial infarction had symptoms consistent with a major depressive episode.^{1 w1 w2} Several studies have shown a link between anxiety disorders and coronary heart disease and between anxiety disorders and hypertension.²

Associations between psychiatric morbidity and cardiovascular disease could simply be attributed to patients being psychologically undermined after diagnosis but this does not explain prospective studies showing excess incidence of cardiovascular problems or poorer cardiovascular outcome in patients with depression and anxiety disorders. One study reported a 3.5-fold increase in mortality of depressed patients compared with non-depressed patients within six months of myocardial infarction.¹ Depression has been associated with the development of cardiovascular complications in patients with hypertension, and several prospective studies have suggested a

Summary points

Anxiety, panic disorder, and depression are common in patients with coronary heart disease and hypertension

There is a plausible biological basis for the association between psychiatric morbidity and cardiovascular disease

Untreated psychiatric disorders worsen the prognosis in patients with cardiovascular problems

Selective serotonin reuptake inhibitors are safe and effective for the treatment of psychiatric morbidity in patients with cardiovascular disease; classic tricyclic agents are best avoided

Treatment with selective serotonin reuptake inhibitors may improve survival after myocardial infarction in patients with depression

Diagnosis and treatment of psychiatric morbidity should be incorporated into the clinical management of coronary heart disease and hypertension

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link between anxiety disorders and subsequent cardiovascular disease or sudden death.^{3 w3}

A biological explanation for the association seems plausible—deficiencies in the central neurotransmitter serotonin may contribute to the development of not only psychiatric morbidity, which may be treated with selective serotonin reuptake inhibitors which increase the availability of serotonin at synapses, but also hypertension and cardiovascular risk (box 2).⁴⁻⁸ Selective serotonin reuptake inhibitors may decrease the risk of a cardiovascular event by reducing platelet activation



Web references w1-w18 are on bmj.com

Box 1: Criteria for depression and anxiety disorders from *Diagnostic and Statistical Manual of Mental Disorders, fourth revision*

Depression

Major depression

Persistent low mood or loss of interest in most activities for at least two weeks, including some of the following, totalling at least five symptoms

- Weight change
- Altered sleep pattern
- Lack of energy
- Poor concentration
- Agitation
- Reduced self esteem
- Suicidal ideas or plans

Minor depression

Three or four symptoms for two or more weeks

Anxiety disorders

General features include

- Autonomic arousal
- Physiological reactivity
- Tremor or shaking
- Avoidance behaviour
- Hypervigilance

Panic disorder

Recurrent spontaneous panic attacks with anticipatory anxiety between attacks and closely associated with agoraphobia

Generalised anxiety disorder

Prolonged periods of excess worry and tension

Post-traumatic stress disorder

Intrusive flashbacks, hypervigilance, and avoidance behaviour after a traumatic stressor

Social anxiety disorder

Fears specific to social situations and characterised by fearfulness, excessive blushing, and avoidance behaviour

or by restoring heart rate variability.^{6,7} Considerable evidence shows autonomic dysfunction in patients with essential hypertension, which may contribute to cardiovascular risk.^{w4} Excess noradrenaline or adrenaline release has also been shown in hypertension and in panic disorder.⁹

Psychological symptoms may impair patients' ability to tolerate or adhere to treatment regimens and to follow interventions to reduce cardiovascular risk. Panic attacks, anxiety, and depression are associated with intolerance to antihypertensive agents, the link being strongest when symptoms reported as side effects are not typical of the drug.¹⁰ Depressed patients are less able to adhere to recommended changes in behaviour and lifestyle after myocardial infarction.^{w5}

Despite this evidence there is poor recognition of anxiety disorders and depression in primary care and hospital medical practice.^{w6} Discriminating symptoms of anxiety or depression from those related to medical conditions can be problematic. Chest pain that commonly occurs in panic attacks can be discriminated from the pain of angina pectoris by location (over the heart rather than beneath the sternum), lack of radiation to the left shoulder or arm, character

(sharp rather than crushing), lack of reproduction with exercise, and duration or frequency at rest.¹¹ Differential diagnoses for non-cardiac chest pain should also be considered, such as microvascular ischaemia (syndrome X) and oesophageal motility disorder.^{w7} Other diagnostic pitfalls include distinguishing transient psychiatric symptoms from those representing major depressive illness or anxiety disorder, and discriminating major depression from minor depression, particularly as minor depression is less responsive to drugs.

Drug treatments for psychiatric morbidity

Many of the treatment strategies of proved efficacy can be prescribed by general practitioners and hospital physicians without the need for referral to a psychiatric specialist. More recently, certain drug treatments for psychiatric morbidity have been associated with reduced incidence of myocardial infarction, and a trend towards improved survival rate after unstable angina and myocardial infarction has been reported.

Efficacy for psychiatric morbidity in the general population

A large evidence base exists for the drug treatment of depression and anxiety disorders in medically fit patients. Antidepressant agents include selective serotonin reuptake inhibitors, tricyclic agents and modified tricyclic agents, and serotonin and noradrenaline reuptake inhibitors. Each of these produces remission in 60-70% of depressed patients when prescribed at a therapeutic dose for six weeks. Some tricyclic antidepressants are effective in panic disorder, but selective serotonin reuptake inhibitors have supplanted them as the drugs of choice and, together with serotonin and noradrenaline reuptake inhibitors, are also effective in other anxiety disorders including generalised anxiety disorder. Benzodiazepines are still commonly used for all anxiety disorders, although prescribers should be aware of their problems.^{w8}

Box 2: Summary of evidence linking serotonin deficiency with cardiovascular risk

- A regimen that increased serotonin in cerebrospinal fluid by over threefold in the cat caused a noticeable increase in ventricular fibrillation threshold and significant reduction in efferent sympathetic activity from the heart¹
- Serotonergic neurones found in the rostral ventral medulla seem to regulate sympathetic outflow⁵
- Heart rate variability, a marker of cardiovascular reactivity that may protect against arrhythmia and cardiac events, is reduced in panic disorder and ameliorated by treatment with selective serotonin reuptake inhibitors⁶
- Selective serotonin reuptake inhibitors may protect against cardiovascular risk through attenuation of platelet activation, even in patients receiving antiplatelet regimens⁷
- The high affinity of most selective serotonin reuptake inhibitors for the serotonin transporter leading to reduced storage of serotonin in platelets has been suggested as an explanation for the cardioprotective action of these drugs⁸

Safety

Concern surrounds the use of tricyclic antidepressants in patients with cardiovascular disease. This is based on adverse effects on contractility shown in animal studies, dysrhythmias and severe hypotension observed after overdose, and electrocardiographic studies that imply a theoretical risk of a pro-arrhythmic action similar to type I antiarrhythmic drugs.^{w9} In contrast, epidemiological and clinical studies, although small, show no worsening of heart failure and no consistent excess of sudden death in normal usage and, if anything, a lower mortality from myocardial infarction than no treatment.^{w10-12} Orthostatic hypotension can be a problem, and in one study almost half the patients with significant heart failure had to withdraw owing to this adverse effect.^{w13} Nortriptyline may be less likely to cause large falls in blood pressure than other tricyclics.^{w14} Concerns about older tricyclics persist and novel tricyclics and selective serotonin reuptake inhibitors might be preferred in patients with pre-existing cardiovascular disease owing to their lower risk potential.

Selective serotonin reuptake inhibitors present fewer concerns over cardiotoxicity as they lack anticholinergic effects, and reports of arrhythmias have been rare. In a double blind comparative study most patients with ischaemic heart disease prescribed the

selective serotonin reuptake inhibitor paroxetine or nortriptyline achieved remission of depressive symptoms, but paroxetine was associated with significantly less cardiovascular side effects.¹²

Patients with cardiovascular disease are likely to be taking other drugs, notably antihypertensives, lipid lowering drugs, and antiarrhythmic drugs, so prescribing selective serotonin reuptake inhibitors is of concern because of possible pharmacokinetic interactions. Many drugs in these classes are metabolised by the cytochrome P-450 enzymes CYP2D6 and CYP3A4. The selective serotonin reuptake inhibitors paroxetine and fluoxetine are potent CYP2D6 inhibitors, whereas fluoxetine and nefazodone are inhibitors of CYP3A4, so these agents can increase plasma concentrations of cardiovascular drugs such as propranolol, metoprolol, flecainide, and encainide metabolised by CYP2D6, and simvastatin, amlodipine, nifedipine, diltiazem, and amiodarone metabolised by CYP3A4, with the potential for more frequent side effects and toxicity. Adverse effects associated with metoprolol occurred five times more frequently in patients with genetically determined low CYP2D6 activity showing that the activity of this enzyme system is clinically important.¹³ Sertraline, citalopram, and tricyclic agents have considerably less potential to

Randomised double blind studies using selective serotonin reuptake inhibitors for psychiatric morbidity in patients with cardiovascular disease

Trial	Psychiatric morbidity	Cardiovascular morbidity	Drugs	No of patients	Cardiovascular adverse effects	Cardiovascular benefit	Psychiatric outcome
Glassman et al (SADHART) 2002 ¹⁴	Major depression*	Myocardial infarction or angina	Sertraline v placebo	369	No significant difference	Non-significant trend, suggesting sertraline protective against subsequent events	Sertraline superior to placebo for most depression outcomes
McFarlane et al 2001 ¹⁵	Major and minor depression by standard questionnaire	Myocardial infarction	Sertraline v placebo	27	Decreased heart rate variability with placebo	Increased heart rate variability with sertraline	Sertraline superior to placebo on depression scores
Strik et al 2000 ¹⁶	Major depression†	Myocardial infarction	Fluoxetine v placebo	54	No significant difference	Non-significant trend, suggesting fluoxetine reduced readmission to hospital for cardiac events	Fluoxetine superior to placebo for most depression outcomes
Roose et al 1998 ¹²	Major depression†	Ischaemic heart disease	Paroxetine v nortriptyline	81	Increased heart rate and decreased heart rate variability with nortriptyline. Significant excess of withdrawals in nortriptyline group due to adverse cardiovascular events (17% v 0%)	—	Paroxetine slightly but not significantly superior to nortriptyline in treatment of depression
Strik et al 1998 ¹⁷	Major depression*	Nil (n=13), myocardial infarction (n=5), and hypertension (n=2)	Fluoxetine v fluvoxamine	20	No significant difference	Ejection fraction improved by both drugs in patients with cardiovascular disease	Both drugs effective in treating depression
Fruehwald et al 2003 ¹⁸	Moderate to severe depression by standard questionnaire	Stroke	Fluoxetine v placebo	50	No cardiovascular effects reported	—	Improvement in depression scores at four weeks in both groups. Fluoxetine superior in open label follow up
Wiarat et al 2000 ¹⁹	Major depression*	Stroke causing hemiplegia	Fluoxetine v placebo	31	No significant cardiovascular effects reported	—	Fluoxetine significantly more effective than placebo for depression
Robinson et al 2000 ²⁰	Major or minor depression*	Stroke	Fluoxetine v nortriptyline v placebo	56	Increase in heart rate significantly greater in nortriptyline group than placebo group	—	Nortriptyline significantly more effective than fluoxetine and placebo for depression and anxiety symptoms
Dam et al 1996 ²¹	Depression by standard questionnaire (severity not stated)	Stroke causing hemiplegia	Fluoxetine v maprotiline v placebo	52	No cardiovascular effects reported; fluoxetine group superior to maprotiline and placebo groups in functional indices	—	Fluoxetine and maprotiline associated with significant improvement in depression
Andersen et al 1994 ²²	Moderate to severe depression by standard questionnaire	Stroke	Citalopram v placebo	66	No serious cardiovascular side effects reported	—	Better outcome in citalopram group

* *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.

† *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised.

inhibit metabolising enzymes than do paroxetine and fluoxetine.^{w15}

The serotonin and noradrenaline reuptake inhibitor venlafaxine may be used in patients with coronary heart disease. Caution is needed at high doses (≥ 300 mg daily) as the drug shows a dose dependent increase in blood pressure averaging 7 mm Hg diastolic at the highest dose.^{w16}

Efficacy for psychiatric morbidity in patients with cardiovascular disease

Until recently there has been a limited evidence base for the efficacy of antidepressants in treating psychiatric morbidity in patients with cardiovascular problems. Evidence now exists for most selective serotonin reuptake inhibitors in five double blind comparative or placebo controlled studies of patients with myocardial infarction, ischaemic heart disease, or hypertension (table).¹²⁻¹⁴⁻¹⁷ In one placebo controlled trial, fluoxetine reduced depression in patients who had had myocardial infarction.¹⁶ Paradoxically only in patients with major depression of mild severity was the treatment effect of fluoxetine significantly greater than that of placebo.

The largest study to date in this area is the SADHART (sertraline antidepressant heart attack randomised trial), a randomised, double blind placebo controlled trial of 369 patients within 30 days of admission to hospital for acute myocardial infarction or unstable angina.¹⁴ The participants had depression at study entry and were assigned to sertraline daily (50-200 mg) or placebo for 24 weeks. Sertraline was as safe as placebo, with no difference in any cardiac safety parameter, but was significantly more effective in treating patients with severe depression and those who had had previous episodes, and produced significantly greater improvement in patient rated global impression scores in the whole sample.

Additional educational resources

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Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanism of interaction. *Biol Psychiatry* 2003;54:248-61.

Roose SP. Treatment of depression in patients with heart disease. *Biol Psychiatry* 2003;54:262-8.

Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99:2192-217.

Information resources for patients

Depression After a Heart Attack (<http://familydoctor.org/handouts/702.html>)—An advice sheet

BBCi Health (http://www.bbc.co.uk/health/ask_doctor/depression_heart.shtml)—General discussion of the link between depression and heart disease

American National Institute of Mental Health (www.nimh.nih.gov/publicat/index.cfm)—Gateway to information sheets about the diagnosis and treatment of common mental disorders

Current and future studies

A trial is in progress to compare the novel serotonin and noradrenaline promoting drug mirtazapine with the selective serotonin reuptake inhibitor citalopram and placebo in depressed patients after myocardial infarction (van den Brink RH, van Melle JP, Honig A, Schene AH, Crijns HJ, Lambert FP, et al. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). *Am Heart J* 2002;144:219-25)

Professor Murray Esler's group at the Baker Medical Institute, Melbourne are currently recruiting for a large trial of selective serotonin reuptake inhibitors in heart disease which will follow on from the SADHART study and allow further quantification of the use of serotonin promoting agents in patients with cardiovascular disease

Professor Robert Carney's group at Washington University are undertaking sleep studies in depressed patients with cardiovascular disease. They plan to explore the hypothesis that reduction in heart rate variability is more pronounced during the night in depressed people leading to greater cardiovascular risk during the nocturnal period. The research may yield further information on how depression can increase the risk of heart attacks in people with cardiovascular disease

Five double blind trials have studied selective serotonin reuptake inhibitors in depressed patients with cerebrovascular disease (see table).¹⁸⁻²² In three, fluoxetine and citalopram were more effective than placebo.¹⁹⁻²¹⁻²² In the fourth, fluoxetine was more efficacious than placebo but only in the open label follow up phase.¹⁸ In the fifth, nortriptyline was superior to fluoxetine and placebo in remission of depressive symptoms.²⁰ In a prophylactic study of 137 patients after stroke, those given sertraline were significantly less likely to experience subsequent depression than those given placebo.²³

Impact of antidepressant treatment on cardiovascular disease

In a case-control study of 5336 patients use of fluoxetine, sertraline, or paroxetine conferred a significantly reduced odds ratio of 0.59 for myocardial infarction.⁸

In the sertraline antidepressant heart attack randomised trial, there was a trend for fewer serious cardiac events in the sertraline group (22.4% v 14.5%), which might suggest a cardioprotective effect in patients with psychiatric morbidity.¹⁴ In an open study, fluoxetine was more effective in lowering blood pressure than the antihypertensive agent moxonidine in hypertensive patients with comorbid panic disorder.²⁴ In contrast, tricyclic agents may increase cardiovascular risk. After adjustment for confounding factors in one observational study, patients who had taken dothiepin were 67% more likely to develop ischaemic heart disease than those who had not used antidepressants.^{w17} In a study of depression after stroke, however, both nortriptyline and fluoxetine were associated with significantly lower overall mortality than placebo when patients were followed up at nine years.²⁵

Non-pharmacological treatments

Substantial evidence supports the use of cognitive behaviour therapy for depression and anxiety disorders in the general population. The technique has also been successful in treating chest pain in patients with negative results on angiography and other cardiac investigations.¹⁸ A recent large study in patients with depression and low perceived social support enrolled within 28 days of myocardial infarction reported that cognitive behaviour therapy improved depression and social isolation but did not reduce subsequent cardiac events.²⁶ Antidepressants were associated with significantly lower mortality or non-fatal myocardial infarction.

Conclusions

Physicians need to recognise psychiatric morbidity, in particular anxiety and depression in patients with coronary heart disease and hypertension. Associations seem to have a biological basis and left untreated psychiatric disorders may worsen the prognosis of patients with cardiovascular problems.

Depression, panic disorder, and generalised anxiety disorder may all be treated effectively with antidepressant drugs. Selective serotonin reuptake inhibitors are safe in patients with cardiovascular disease, but indirect evidence suggests that classic tricyclic agents are best avoided. With recent evidence suggesting that selective serotonin reuptake inhibitors may improve survival after myocardial infarction in patients with depression, diagnosis and treatment of psychiatric morbidity should be incorporated into the clinical management of hypertension and coronary heart disease.

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