What is the antidepressant of choice in coronary heart disease?

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Background

Approximately 20% of patients with coronary heart disease (CHD) have major depression and 20% have minor depression at any given point in the course of their illness (1). Depression causes significant psychological and social morbidity, and is a risk factor for further cardiac morbidity and mortality (1). Effective treatment of depression in these patients is therefore vital and it has been suggested that some antidepressants may protect against Myocardial Infarction (MI) (2). However, given that most antidepressants have a potential for adverse cardiovascular effects which could in turn increase cardiac morbidity, the choice of agent for patients with CHD cannot be based on effectiveness alone. NICE have recently published guidance on depression in adults with chronic physical health problems which makes recommendations on suitable antidepressants in these patients (3).

Answer

The choice of antidepressant depends on an assessment of the individual patient. The prescriber needs to take into account the risk: benefit ratio of treatment, type and severity of the depression and the cardiovascular disease, patient preference, past experience and the individuals’ characteristics when choosing which agent to use.

There have been relatively few trials that have studied the use of antidepressants in patients with cardiac disease. The main groups of agents that have been included in these trials are the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs). There is limited data on the second and third generation antidepressants. Monoamine oxidase inhibitors (MAOIs) are infrequently prescribed in the UK due to their potential for serious drug interactions and the availability of safer antidepressants. There is a lack of data on their use in patients with cardiac disease.

Selective Serotonin Reuptake Inhibitors

SSRIs are safer than TCAs with regard to the risk of cardiovascular side effects (4-6). In general, SSRIs appear to have little or no effect on blood pressure or heart rhythm. However, there are case reports of prolonged QTc interval, first-degree block, and postural hypotension in SSRI-treated patients (4). It has also been suggested that the use of SSRIs in depressed patients who have experienced an acute MI might reduce subsequent cardiovascular morbidity and mortality but this requires further study (2;7).

A cautionary statement relating to SSRI use in cardiac patients is present on the Summary of Product Characteristics (SPCs) for fluoxetine, escitalopram, paroxetine and fluvoxamine (8-11) and the SPC for citalopram mentions that increased levels of a minor metabolite could theoretically prolong the QTc interval in susceptible individuals (12). However the SPC for sertraline does not carry a caution for use in cardiac patients (13).

Clinical trials

Paroxetine (20-40mg daily) (n=41) was compared to nortriptyline (started at 25mg daily and adjusted according to plasma levels) (n=40) over a six week period, in patients with both depression and CHD and demonstrated comparable efficacy in terms of antidepressant effect but with a lower incidence of serious cardiac events (defined as increased heart rate, raised blood pressure, reduced ejection fraction and conduction problems) (14).

Up to 60mg daily of fluoxetine has been studied in a small population of depressed patients with pre-existing cardiac disease (n=27), which included congestive heart failure, conduction disorders and ventricular arrhythmias. Fluoxetine was not found to have any significant adverse cardiovascular


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effects over 7 weeks when compared to nortriptyline (n=60) (15). Limitations of these two studies are their short duration and small patient populations. The studies may not have had sufficient power to detect all adverse cardiovascular events. Fluoxetine has also been studied over a longer period of time (25 weeks), in a small placebo-controlled trial, in patients with depression and who had a recent MI (n=54). A dose of up to 60mg/day was used. No significant changes in any cardiovascular markers were noted (16).

In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), sertraline (50-200mg/day) (n=186) was reported to be a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina over 24 weeks when compared to placebo (n=183) (17). Treatment with sertraline was not associated with any worsening of left ventricular function, blood pressure, heart rate, or with an increase in ventricular arrhythmias or QT interval prolongation (17) (18). Patients receiving sertraline had fewer severe cardiac events such as death, MI, worsened angina and/or onset of congestive heart failure compared with patients taking placebo (18).

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) randomised trial investigated whether treating depression could improve cardiac prognosis in patients following myocardial infarction (1:4). A total of 2,481 patients with depression, low perceived social support or both were assigned to cognitive behavioural therapy or usual care. In addition, SSRI therapy (mainly sertraline 50mg daily, adjusted up to 200mg daily if needed) was added to cognitive behavioural therapy in severely depressed patients unresponsive to the initial therapy. The results showed there was a reduction in depression and improvement in social support, but the study treatments did not affect the likelihood of recurrent myocardial infarction or death from any cause (the primary, or composite, endpoint). However, a secondary analysis of the ENRICHD study, found a significantly lower risk of mortality and recurrent infarction in patients who received antidepressants, especially SSRIs, compared with patients who received psychotherapy only or no treatment. This result may not be reliable as antidepressant therapy was not allocated by random assignment (1:4).

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial (n=284) evaluated the efficacy and tolerability of citalopram (20-40mg/day) and interpersonal psychotherapy over 12 weeks in patients with depression and coronary artery disease (19). The study found that citalopram was well tolerated and effective in treating moderate to severe depression in patients with coronary artery disease; there were no differences between citalopram and placebo in any blood pressure or electrocardiographic measures, including QT intervals (19). The cardiac safety of citalopram has also been studied in both prospective and retrospective studies of 1789 citalopram-treated patients (20). The only effect of citalopram was the reduction in heart rate but no other ECG changes were noted. There have been case reports of bradycardia with citalopram and a low frequency of hypotension and arrhythmias including left bundle branch block (20).

**Escitalopram** should be used with caution in patients with coronary heart disease and cases of QT-prolongation have been reported during the post-marketing period (9). It is assumed to have similar cardiac side effects as citalopram but results from further studies are needed (2).

**Fluvoxamine** has a minimal effect on heart rate and blood pressure and no significant effect on the QTc interval. Limited changes in ECG have been observed and it should be used with caution post-MI (2).

**Drug interactions**

The other aspect that needs to be considered is the potential for interactions with the SSRIs. Some SSRIs inhibit certain isoenzymes of the cytochrome P450 system and have the potential for drug-drug interactions with various medicines (2;4), which is an important issue in cardiac patients who are likely to be on multiple medications. NICE recommends in patients with depression and a chronic physical health problem to consider using citalopram or sertraline as these have a lower propensity for interactions (3). SSRIs also increase the risk of gastrointestinal (GI) bleeding. They have an inhibitory effect on platelets and reduce clot formation, leading to an increase in the risk of an upper GI bleed to a slightly lower extent (1 in 300 patient years) than that seen with non-steroidal anti-inflammatory drugs (NSAIDs) (1 in 200 patient years) (21). Of particular concern would be the concomitant use of SSRIs with the antiplatelet agent aspirin; concurrent use with NSAIDs has been shown to increase the risk of

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gastrointestinal bleeds (1 in 80 patient years), particularly in the elderly and those with a previous history of GI bleed (21). The concurrent use of SSRIs with aspirin and NSAIDs is cautioned on all of the SPC’s of the SSRIs (8-13). In addition, the inhibitory effect on platelet aggregation may increase the risk of haemorrhagic stroke, a concern that has yet to be seen in practice (22).

**Summary for SSRIs**

Most researchers have concluded that SSRIs are generally safe and well tolerated in patients with CHD when appropriate precautions are taken (1). This is based on the relatively low incidence of cardiac adverse effects in patients with depression without heart disease and the results of the few available studies of patients with depression and CHD (1). NICE recommends that generally SSRIs should be first-line treatment for depression associated with physical illness (3). Of the SSRIs, sertraline and citalopram probably have the lowest interaction potential, appear to be safe and possibly protective of further cardiac events so generally should be the drugs of first choice (3). However, citalopram has a minor metabolite which may increase the QTc interval and it has been linked to a risk of torsades de pointes (2). Sertraline is considered the drug of choice post-MI in the Maudsley Guidelines (2).

**Tricyclic Antidepressants**

These are the most extensively studied antidepressants with respect to cardiovascular effects. They are known to increase heart rate, cause postural hypotension, slow cardiac conduction and have class 1 antiarrhythmic activity (2;4). The original concern over the use of TCAs post-MI stemmed from the Cardiac Arrhythmia Suppression Trials (CAST I and II studies), which demonstrated that treatment of ventricular arrhythmias after MI with class I antiarrhythmic drugs is associated with a substantial increase in sudden death during ischaemic episodes (23;24). As a result, both CAST I and II were stopped early. Due to the class I antiarrhythmic action of the TCAs they are best avoided in patients with CHD, and are considered contraindicated in patients who have had a recent MI (2;4;6;18).

NICE advises that tricyclics should be avoided as first line treatment in patients with depression and chronic health problems. When choosing an antidepressant for patients at risk of suicide, toxicity in overdose should be taken into account. TCAs, except for lofepramine, are associated with the greatest risk in overdose. Dosulepin has marked toxicity in overdose and should not be prescribed (3;20).

**Other antidepressants**

The drawback with all other antidepressants is the lack of studies in patients with cardiac disease. Due to the limited data, these agents should not be considered first line treatment unless an SSRI is contraindicated or otherwise unsuitable in an individual patient.

(1) **Second-generation antidepressants**

Trazodone is generally considered to have a low cardiotoxicity risk but it has only been studied in very small numbers of patients with depression and cardiac disease (16;20). There have been reports of arrhythmias, postural hypotension and prolongation of the QT interval (2;20). The advice is to use trazodone with care in patients with severe cardiac disease (2;25).

Mianserin is also considered to have a low cardiotoxicity risk(6) and cardiac effects are rare (20). There have been some reports of bradycardia and complete heart block in overdose and rarely bradycardia at therapeutic doses (20). It is considered a suitable alternative when SSRIs are contraindicated (3).

(2) **Third-generation antidepressants**

The Myocardial Infarction and Depression-Intervention Trial (MIND-IT) investigated the effectiveness of active antidepressant treatment versus ‘usual care’ in patients with post-MI major and minor depressive disorder (26). The intervention arm (n=47) was a double blind, randomised controlled study comparing the safety and efficacy of mirtazapine (30-45mg) with placebo over 24 weeks (27). The primary end point was the occurrence of any significant cardiac event (including cardiac death, hospital admission for non-fatal MI, coronary artery bypass grafting, heart failure, or ventricular tachycardia). The trial failed to find any significant difference in the treatment effect on the patients’ depression or in the incidence of adverse cardiac effects. The SPC for mirtazapine carries a caution in patients with angina or a recent MI (28). However, mirtazapine is a suitable alternative to SSRIs in cardiac disease (2;3).
No studies looking at the use of reboxetine or moclobemide in patients with cardiac disease have been identified. Significant increases in heart rate have been seen with reboxetine and orthostatic hypotension has occurred at higher doses (2;6;29). Cases of hypertension have been reported with moclobemide and it has been seen to cause marginal decreases in heart rate (2;6). Reboxetine is cautioned in patients with cardiac disease (2).

There is limited clinical experience with duloxetine use in patients with cardiac disease and no studies of its use in cardiac patients have been identified (2). It can cause clinically significant hypertension and is contraindicated in patients with uncontrolled hypertension (30). Blood pressure monitoring in patients with known hypertension and/or other cardiac disease is advised. Duloxetine should be used with caution in patients with recent MI (2).

In the UK, venlafaxine is no longer subject to excessive MHRA and SPC restrictions. It is only contraindicated in patients with an identified high risk of a serious cardiac ventricular arrhythmia or with uncontrolled hypertension (but is not contraindicated in controlled hypertension) (6). There is a caution for use in established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction). No baseline ECG is needed but regular blood pressure monitoring is recommended (6). NICE has advised that compared with other equally effective antidepressants, venlafaxine is associated with a greater risk of death from overdose (3).

Summary

- Data on the use of antidepressants in patients with coronary heart disease (CHD) are limited.
- SSRIs are the agents of choice in CHD. Although there is limited data, they are generally safe and well tolerated in patients with CHD when appropriate precautions are taken (1).
- Tricyclic antidepressants have the most data on their use in depression but are known to be cardiotoxic. Therefore, TCAs are best avoided in patients with CHD and are contraindicated in patients who have had a recent MI. NICE advises that tricyclic antidepressants, except for lofepramine, are associated with the greatest risk in overdose.
- Potential interactions with the SSRIs should be taken into account when prescribing in CHD. NICE recommends for people with depression who also have a chronic physical health problem to consider using citalopram or sertraline as these have a lower propensity for interactions.
- Sertraline is safe post MI and considered the drug of choice in these patients (2).
- Mirtazapine is a suitable alternative in cardiac disease if SSRIs cannot be used but it should be used with caution. There is evidence of safety post MI.
- Venlafaxine is contraindicated in patients with an identified high risk of a serious cardiac ventricular arrhythmia or with uncontrolled hypertension. It should be used with caution in established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction). Venlafaxine is associated with a greater risk of death from overdose compared with other equally effective antidepressants.

Limitations

The majority of trials have involved a small sample size and have been relatively short term, therefore long-term safety data is lacking (3;5).

The choice of antidepressant to use still depends on the clinician assessing individuals on a case-by-case basis. They need to consider:

- The severity and type of cardiovascular disease and depression
- The individual’s characteristics
- Previous and current drug/medical history
- The side effect profile of the individual antidepressants
Disclaimer

- Medicines Q&As are intended for healthcare professionals and reflect UK practice.
- Each Q&A relates only to the clinical scenario described.
- Q&As are believed to accurately reflect the medical literature at the time of writing.
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References


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Search strategy

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- Embase [terms used: depression (exp), antidepressant agent (exp), ischemic heart disease (exp), limited to since Jan 2006, English, Human and Adult.]
- Medline [terms used: heart diseases(exp), myocardial ischemia (exp), antidepressive agents (exp), Moclobemide, free text terms = venlafaxine, reboxetine, mirtazapine, duloxetine, escitalopram and flupenthixol]
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