What is the antidepressant of choice in coronary heart disease?

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Published: April 2012

Summary

- Data on the use of antidepressants in patients with coronary heart disease (CHD) are limited.
- SSRIs are the agents of choice in CHD. They are generally well tolerated, effective and safe to use in patients with CHD when appropriate precautions are taken. Sertraline is safe post MI and considered the drug of choice in these patients. However, citalopram is associated with dose-dependent QT interval prolongation and is contra-indicated in patients with known QT interval prolongation or congenital long QT syndrome. It is also cautioned in patients at higher risk of developing Torsades de Pointes.
- Tricyclic antidepressants are best avoided in patients with CHD and are contraindicated in patients who have had a recent MI. TCAs are viewed as highly cardiotoxic in overdose and may therefore worsen outcome in CHD patients
- Mirtazapine is a suitable alternative in CHD if SSRIs cannot be used but it should be used with caution. There is evidence of safety post MI.
- 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 sertraline as this has a lower propensity for interactions.
- 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 MI). Venlafaxine is associated with a greater risk of death from overdose compared with other equally effective antidepressants.

Background

Depression occurs frequently in patients with coronary heart disease (CHD) and is associated with poor prognosis (1). Approximately 20% of patients with CHD have major depression and 20% have minor depression at any given point in the course of their illness (2). Depression causes significant psychological and social morbidity, and is a risk factor for further cardiac morbidity and mortality (2). Effective treatment of depression in these patients is therefore vital and it has been suggested that some antidepressants may protect against Myocardial Infarction (MI) (3). 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 published guidance on depression with chronic physical health problems which makes recommendations on suitable antidepressants in these patients (4;5).

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 also some 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

Selective Serotonin Reuptake Inhibitors

SSRIs may have a small yet clinically meaningful effect on depression outcomes in CHD patientsand are possibly protective against MI (1;3). They are safer than TCAs with regard to the risk of cardiovascular side effects and are generally recommended in cardiac disease but beware of cytochrome-mediated drug interactions with co-administered cardiac drugs (3;6). NICE recommends that generally SSRIs should be first-line treatment for depression associated with physical illness. Of the SSRIs, sertraline and citalopram probably have the lowest interaction potential (3). However, citalopram is associated with dose-dependent QT interval prolongation and is contra-indicated in patients with known QT interval prolongation or congenital long QT syndrome (7).

A cautionary statement relating to SSRI use in cardiac patients is present on the Summary of Product Characteristics (SPCs) for fluoxetine, escitalopram, paroxetine, fluvoxamine and citalopram (8-11). Citalopram is cautioned in patients at higher risk of developing Torsade de Pointes, such as those with congestive heart failure, recent MI, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia. Doses higher than citalopram 40mg daily should be avoided (3;7).The SPC for sertraline does not carry a caution for use in cardiac patients and sertraline is considered the drug of choice post-MI in the Maudsley Guidelines (3;12).

NICE advises to take into account the fact that SSRIs increase the risk of gastrointestinal (GI) bleeding (4). They have an inhibitory effect on platelets and reduce clot formation, leading to an increase in the risk of an upper GI bleed (13). Concomitant use of SSRIs with the antiplatelet agent aspirin, and concurrent use with NSAIDs has been shown to increase the risk of gastrointestinal bleeds, particularly in the elderly and those with a previous history of GI bleed(13). The concurrent use of SSRIs with aspirin and NSAIDs is cautioned on all of the SPC's of the SSRIs (7-13).

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 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 (2;6). 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 (2;6).

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). However, note that during the post-marketing period citalopram has been found to cause a dose-dependent prolongation of the QT-interval and is contra-indicated in patients with known QT interval prolongation or congenital long QT syndrome (7).

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 (8). It is assumed to have similar cardiac side effects as citalopram but results from further studies are needed (3).

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 (3).

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 (3;6). 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 (3;6;).

TCAs are viewed as highly cardiotoxic in overdose and may therefore worsen outcome in CHD patients (1).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 (4;5).

Other antidepressants

(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 (5;16). There have been reports of arrhythmias, postural hypotension and prolongation of the QT interval (3;5,20). Trazodone should be used with caution in patients with cardiac disease, such as angina pectoris, conduction disorders or AV blocks of different degree, or recent myocardial infarction (20).

Mianserin is also considered to have a low cardiotoxicity risk(21) and cardiac effects are rare (5). There have been some reports of bradycardia and complete heart block in overdose and rarely bradycardia at therapeutic doses (5).

(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 (22). 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 (23). 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 (24). However, mirtazapine is a suitable alternative to SSRIs in cardiac disease (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 (3;25). Cases of hypertension have been reported with moclobemide and it has been seen to cause marginal decreases in heart rate (3).Reboxetine is cautioned in patients with cardiac disease (3;25).

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 (3). It can cause clinically significant hypertension and is contraindicated in patients with uncontrolled hypertension (26). 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(3).

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) (21). There is a caution for use in established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent MI). No baseline ECG is needed but regular blood pressure monitoring is recommended (21). NICE has advised that compared with other equally effective antidepressants, venlafaxine is associated with a greater risk of death from overdose (4).

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;). 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

References

(1) Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease (review). 2011. The Cochrane collaboration. John Wiley & Sons Ltd.

(2) Carney RM, Freedland KE, . Depression in patients with coronary heart disease. Am J Med 2008; 121:S20-S27.

(3) Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 11th ed. Oxford. Wiley-Blackwell, 2012.

(4) National Collaborating centre for mental health, commissioned by NICE. Depression in adults with a chronic physical health problem: treatment and management. National Clinical Practice Guideline 91. October 2009 Date accessed 23/04/2012 Accessed via www.nice.org.uk

(5) National Collaborating centre for mental health, commissioned by NICE. Depression in adults (update): the treatment and management of depression in adults. Full guidance. National Clinical Practice Guideline 90. October 2009. Accessed via www.nice.org.uk Date accessed 23/04/2012

(6) Anon. Depression, antidepressants and heart disease. Drug Ther Bull 2008; 46(4):29-32.

(7) Summary of Product Characteristics. Cipramil 10, 20 and 40mg film coated tablets. Lundbeck Limited. Accessed via www.emc.medicines.org.uk Date accessed 12/04/2012 Date of revision of text 23/01/2012

(8) Summary of Product Characteristics. Cipralex 5, 10 and 20mg film coated tablets and 10mg/ml and 20mg/ml oral drops, solution. Lundbeck Limited. Accessed via www.emc.medicines.org.uk Date accessed 12/04/2012 Date of revision of text 16/12/2011

(9) Summary of Product Characteristics. Faverin 50mg film coated tablets. Abbott Healthcare Products Limited. Accessed via www.emc.medicines.org.uk Date accessed: 12/04/2012 Date of revision of the text: 01/03/2012

(10) Summary of Product Characteristics. Prozac 20mg hard capsules and 20mg per 5ml oral liquid. Eli Lilly and Company Limited Accessed via www.emc.medicines.org.uk Date accessed: 12/04/2012 Date of revision of the text: 09/03/2012

(11) Summary of Product Characteristics. Seroxat tablets 10mg, 20mg, 30mg tablets, 20mg/10ml oral suspension. GlaxoSmithKline UK. Accessed via www.emc.medicines.org.uk Date accessed: 12/04/2012 Date of revision of the text: 01/07/2011

(12) Summary of Product Characteristics. Lustral. Pfizer Limited. Accessed via www.emc.medicines.org.uk Date accessed: 12/04/2012 Date of revision of text: Feb 2012

(13) Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding (editorial). BMJ 2005; 331:529-530.

(14) Roose SP, Laghrissi-Thode F, Kennedy JS et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998; 279(4):287-291.
(15) Roose SP, Glassman AH, Attia E et al. Cardiovascular effects of fluoxetine in depressed patients with heart disease. Am J Psychiatry 1998; 155(5):660-665.
(16) Alvarez W, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: A review of the literature. Pharmacotherapy 2003; 23(6):754-771.
(17) Glassman AH, O'Connor CM, Califf RM et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002; 288(6):701-709.
(18) Jiang W, Glassman A, Krishnan R et al. Depression and ischemic heart disease: What have we learned so far and what must we do in the future? Am Heart J 2005; 150(1):54-78.
(19) Lesperance F, Frasure-Smith N, Koszycki D et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease. JAMA 2007; 297(4):367-379.
(20) Summary of Product Characteristics. Molipaxin 50mg Capsules. Winthrop Pharmaceuticals UK Ltd. Accessed via www.emc.medicines.org.uk Date of access: 23/04/2012 Date of revision of the text: 27/09/2010
(21) Bazire S. Psychotropic Drug Directory 2012. Warwickshire. Lloyd-Reinhold Communications, 2012.
(22) van Melle JP, de Jonge P, Honig A et al. Effects of antidepressant treatment following myocardial infarction. Br J Psychiatry 2007; 190:460-466.
(23) Honig A, Kuyper AMG, Schene AH et al. Treatment of post-myocardial infarction depressive disorder: A randomized, placebo controlled trial with mirtazapine. Psychosom Med 2007; 69:606-613.
(24) Summary of Product Characteristics. Zispin SolTab 15mg, 30mg, and 45mg orodispersible tablets. Merck Sharp & Dohme Limited. Accessed via www.emc.medicines.org.uk Date of access: 12/04/2012 Date of revision of the text: Oct 2010
(25) Summary of Product Characteristics. Edronax 4mg tablets. Pharmacia Limited. Accessed via www.emc.medicines.org.uk Date of access: 12/04/2012 Date of revision of the text: Sept 2011
(26) Summary of Product Characteristics. Cymbalta 30mg hard gastro resistant capsules, Cymbalta 60mg hard gastro resistant capsules. Eli Lilly and Company Limited Accessed via www.emc.medicines.org.uk Date of access: 12/04/2012Date of revision of the text: 26/07/2011
(27) Bostwick J. The heart of depression: Treating patients who have cardiovascular disease. Current Psychiatry 2011;10 (1):31-34.

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Date Prepared

Full update 12th April 2012

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Date of check

03/05/2012

Search strategy

- 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]
- In-house Database/resources
- eMC
- NICE
- MHRA