Treatment of depression in heart failure

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Drugs & Therapeutic Committee

Year of approval

2021

Responsible owners

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Review date

3 years after approval

DTC code

2021/32

The Quality Centre is how we work with staff, patients, and carers, alongside colleagues at Kings College London and Kings Health Partners, to drive improvement, innovation and value-based commissioning in mental health care. All our work is underpinned by the principles of collaboration, inclusion, shared learning and the use of data intelligence to achieve our vision of optimising health outcomes for the populations we serve, whilst bringing together our learning for wider benefit.

Treatment of depression in heart failure

Contents

1 Introduction

1.1 Scope

This guideline makes treatment recommendations for adults aged 18 and over, diagnosed with depression, who have a diagnosis of heart failure +/- comorbidities.

This guideline does not cover:

- Diagnosis of depression
- Non-pharmacological treatments
- Treatment-resistant depression
- Non-depressive symptoms (e.g. psychosis)

1.2 Treatment of depression

Depression is characterised by a depressed mood and/or loss of pleasure in most activities[1]. In general, antidepressants are not recommended as a first-line treatment for recent-onset, mild depression[1]. For patients with moderate to severe depression, antidepressants should be prescribed.

NICE recommend choosing a generic selective serotonin reuptake inhibitor (SSRI) first-line. Choice of drug should be based on patient preference, likelihood of side effects, and potential for interactions with concurrent medications or comorbidities. In an absence of any medical considerations, sertraline, fluoxetine, citalopram and escitalopram are generally considered reasonable choices[1].

Approximately a third of patients will fail to respond to the first antidepressant[2]. The usual treatment strategy at this point is to switch to a different SSRI or to trial a serotonin and noradrenaline reuptake inhibitor (SNRI) or mirtazapine[1]. Following failure of a second antidepressant, effect sizes from further drug switches, or use of augmenting medications (commonly antipsychotics or mood stabilisers) are modest and diminishing[3]. Patients at this stage of their illness are usually described as suffering from 'treatment-resistant' depression and are beyond the scope of this guideline. Advice from specialist psychiatric services should be sought.

1.3 Treatment of heart failure

Patients with heart failure and a reduced ejection fraction usually receive an angiotensin-converting enzyme inhibitor (ACEI) first line, and a beta-blocker. If the ACEI is not tolerated, an angiotensin-II receptor blocker (ARB) may be considered.

If the patient remains symptomatic despite optimisation of the ACEI/ARB and beta-blocker, a mineralocorticoid receptor antagonist (MRA) or aldosterone receptor antagonist (AA) is added. Further options for patients still symptomatic after these interventions include sacubitril/valsartan, ivabradine, digoxin, hydralazine, and nitrates. Sodium-glucose co-transporter-2 (SGLT2) inhibitors (dapagliflozin, canagliflozin, empagliflozin) have also recently been licensed for patients with heart failure with or without diabetes.

All patients may require diuretics (loop and sometimes thiazides) for symptomatic relief, at any stage of their illness.

The treatment of patients with heart failure with a preserved ejection fraction is focussed on treating underlying comorbidities and providing symptomatic relief with diuretics.

1.4 Treatment of depression in heart failure

As many as one in five patients with heart failure will also suffer with depression, more than doubling the mortality risk[4] and trebling the risk of non-compliance with medical treatment recommendations[5].

Systematic review of randomized controlled trials of antidepressants in chronic physical health conditions finds antidepressants to be generally effective, with effect sizes broadly similar to that see in the medically well population[6]. There are few data for the efficacy of pharmacotherapy in depression specifically with comorbid heart failure. When extrapolating data from studies in patients without heart failure, it should be noted that populations studied in these trials are different (heart failure patients tend to be older than populations with general depression). Additionally, the biological symptoms of depression that are measured by standard depression rating scales may not appear to improve on addition of antidepressants, because of overlap of these signs with ongoing symptoms of heart failure (e.g. Fatigue). It is also possible that depression in heart failure is biologically distinct from general depression and antidepressants may not be effective for this reason.

Decisions on the treatment of depression in patients with heart failure are therefore largely based on efficacy data from the non-heart failure population, the likelihood of adverse effects that would worsen the symptoms of heart failure and/or comorbid conditions, and the likelihood of drug interactions with medicines usually prescribed for heart failure and/or comorbid conditions.

1.5 Aims of treatment

The aim of the use of antidepressants to treat depression in patients with comorbid heart failure is to provide relief of depressive symptoms, with minimal or no adverse effect on the symptoms of the heart failure or interactions with the medications used to treat the heart failure.

1.6 General points on antidepressants

1.6.1 Time to response

The degree of improvement in depressive symptoms in response to antidepressant treatment is highest in the first 1 – 2 weeks, reducing from there to the lowest rate during weeks 4 – 6. In clinical practice, antidepressant effects in individual patients are usually seen within the first two weeks[7]. If there is no response by weeks 3 – 4, any latent response is highly unlikely to emerge and it is recommended that a treatment switch be considered[2]. Note that time to response in elderly patients or those with treatment-resistant illness may be longer

1.6.2 Duration of treatment

Antidepressants should be taken for 6 – 9 months *after recovery* from a single episode of depression. For patients who have had multiple episodes of depression, treatment should be continued for at least 2 years, but probably longer[2].

Time to response	Comment
1-2 weeks	Degree of improvement highest
3-4 weeks	If no response then switch
4-6 weeks	Lowest response rate
6-9 months	After **recovery** of single episode, can be reviewed/stopped.
2 years	After multiple episodes continue for a minimum of 2 years.

Table 1: summary of response times for antidepressants.
Note that time to response in elderly patients or those with treatment-resistant illness may be longer

2 Recommendations

2.1 Heart failure

In general, SSRIs are considered first-line choice antidepressants, and this is also true for patients with heart failure. Of the SSRIs, sertraline[2,8] is generally well tolerated and efficacious in non-heart failure populations[1,9]. It has few drug interactions, less propensity than citalopram to prolong the QTc, and has been studied in patients with heart failure (it is safe, but efficacy is unproven)[10]. Escitalopram has also demonstrated safety (although not efficacy) in patients with heart failure[11], but may be more associated with QTc prolongation[12] than sertraline (note this association is disputed[13]). Other options carry some cautions. Mirtazapine is consistently shown to promote appetite, probably due to α_2 receptor blockade and affinity for H_1, D_1 and D_2 receptors[14], and is therefore less desirable in conditions such as heart failure where excess weight is detrimental to clinical outcomes. Citalopram may be more likely than other antidepressants to prolong the QTc interval, and is not recommended for use in uncompensated heart failure[15]. SNRIs (venlafaxine and duloxetine) are associated with dose-dependent increases in blood pressure[16] (but see section on comorbid hypertension below), and venlafaxine and fluoxetine may also cause prolonged QTc, particularly in combination with ivabradine[4]. Tricyclic antidepressants (TCAs) are generally avoided in patients with cardiac disease due to their effects on cardiac contractility, proarrhythmic effects (due to blockade of cardiac sodium and potassium channels), and potential to worsen ischaemic heart disease.

Hyponatraemia is a risk with all antidepressants. ACEI can cause SIADH and hyponatraemia. Diuretics and sacubitril must be discontinued if hyponatraemia develops. Mirtazapine and agomelatine may be less associated with hyponatraemia (but are not completely without risk). Close monitoring of sodium levels is recommended, especially in the first few weeks of treatment[17] and if patients have additional risk factors for developing hyponatraemia.

Recommendation: sertraline

Drug	Comments
Sertraline	Well tolerated, few interactions, efficacious. Less propensity to prolong the QTC
Escitalopram	Demonstrated safety but not efficacy, maybe more likely to cause QTC prolongation.
Mirtazapine	Causes appetite increase, increased weight less is detrimental, it less likely to cause hyponatraemia.
Citalopram	More likely to prolong the QTC, not recommended.
SNRI's (venlafaxine & Duloxetine)	Associated with dose dependant increases in B.P. Venlafaxine also causes prolonged QTC.
Fluoxetine	May cause prolonged QTC.
Tricyclics	Should be avoided due to adverse cardiac effects.
Agomelatine	Less likely cause hyponatraemia.

Table 2: summary of antidepressant medication in heart failure

The following sections make recommendations on the pharmacological treatment of depression where heart failure coexists with other medical conditions.

2.2 Ischaemic heart disease

Ischaemic heart disease (IHD) is the most common comorbidity in patients admitted to hospital in acute heart failure[18]. TCAs should be avoided in patients with IHD for the reasons outlined in section 2.1 – trial evidence also demonstrates negative cardiac outcomes for patients with IHD taking TCAs (increased heart rate, reduction in heart rate variability, and increased pulse[19,20]). The safety of SSRIs and mirtazapine post-MI has been demonstrated in several landmark studies[10,21,22], and it has further been suggested that the inhibitory effect of SSRIs on platelet activation may actually protect against MI[23]. This potential benefit (studies thus far have been underpowered to confirm this claim[10]) must be balanced against the increased risk of bleeding and gastric irritation when co-prescribing serotonergic antidepressants with aspirin or other antiplatelet therapies. A patient-centred approach is suggested – mirtazapine may be preferred over sertraline if the patient is felt to be at significant increased risk of bleeding, but balance this with the increased longer-term risk of weight gain with mirtazapine.

Recommendation: sertraline, or mirtazapine if significant bleeding risk

2.3 Hypertension

Hypertension and depression may share some pathology - both may involve overactivation of the sympathetic nervous system. Blockade of noradrenergic receptors in the heart, as well as centrally, may further sensitise the heart to sympathetic activation, increasing cardiac output and blood pressure[24]. This may be further exacerbated by drugs that block noradrenaline receptors, such as TCAs and SNRIs. Indeed, TCAs (and MAOIs) are associated with a risk of hypertensive crisis, and noradrenergic drugs (venlafaxine, duloxetine) are associated with dose-dependent increases in blood pressure[25] (although the effect for venlafaxine is not clinically significant at doses below 200mg/day, and even above this is only significant for about 5% of patients[26]). The anticholinergic effects of drugs such as TCAs may also contribute to increases in systolic blood pressure[25]. None are recommended for patients with pre-existing hypertension.

SSRIs do not appear to affect blood pressure[27], and are therefore preferable.

Recommendation: sertraline

2.4 Anticoagulation

Serotonergic antidepressants are associated with an increased risk of bleeding (not restricted to gastrointestinal bleeds), and this is likely to be related to the affinity of the drug for the serotonin transporter on platelets. Drugs that have weak (or no) affinity for the serotonin transporter are preferred for patients at risk of bleeding, including those taking concurrent anticoagulants. Options include trazodone, mianserin, reboxetine, dosulepin, moclobemide, nortriptyline, phenelzine, trimipramine, lofepramine, mirtazapine and agomelatine. Trazodone and mianserin are recommended by NICE[28], but trazodone may increase digoxin levels[29]. Reboxetine is not effective and there is a risk of hypokalaemia and hypocalcaemia when it is given with diuretics[29]. TCAs are proarrhythmic, and TCAs and MAOIs associated with an increased risk of hypertension. Mirtazapine and agomelatine are probably safer alternatives, although note the risk of weight gain with mirtazapine described in section 2.1. Mirtazapine is reported to potentially cause small increases in the INR, but this is not considered clinically significant.

Recommendation: mirtazapine or agomelatine

2.5 Atrial fibrillation

There are several considerations for patients with atrial fibrillation and heart failure who require an antidepressant. First is to avoid contributing to the arrhythmia itself, or to cause other effects that would worsen the clinical consequences of an arrhythmia. Second, patients with atrial fibrillation will also be taking anticoagulation. Further consideration may be made of the likelihood of QTc prolongation, and the potential consequence of this for individuals. TCAs increase the risk of bradycardia, are arrhythmogenic, have the potential to increase the QTc, and affect cardiac contractility[4]. SSRIs do not appear to cause incident arrythmia[30], but do contribute to the risk of bleeding for patients on anticoagulants (see section 2.4). The SSRIs may cause dose-dependent QTc increases, but this is clinically insignificant for most (citalopram and escitalopram may be the exceptions, although this is disputed)[31]. Vortioxetine and agomelatine are not known to affect the QTc[32], but vortioxetine carries a moderate risk of bleeding. Mirtazapine and sertraline are shown to be safe post-MI [33,34], a population at increased risk of arrhythmias.

Recommendation: mirtazapine or agomelatine

2.6 Stroke

SSRIs and nortriptyline are widely recommended as the antidepressants of choice post-stroke[32]. SSRIs however are problematic to use in patients also taking anticoagulation (inevitable if the stroke was ischaemic) or at risk of bleeding for other reasons (potentially those who suffered haemorrhagic stroke), as outlined in section 2.4. Nortriptyline is more attractive in this regard, but TCAs generally are avoided in heart failure, see section 2.1. Mirtazapine and agomelatine largely avoid issues with bleeding, but data supporting use post-stroke are entirely lacking for agomelatine, and conflicting for mirtazapine. One cohort study suggested an increased risk of a second stroke with mirtazapine, although this was in older adults, and the risk appears to reduce with time – this may reflect the fact that undertreated depression itself is a risk factor for stroke[35]. Other studies support the safety and efficacy of mirtazapine post-stroke[36,37].

Recommendation: mirtazapine

2.7 Dementia

Vortioxetine a low anticholinergic burden[38], has been studied in older populations[39] and may have additional benefits for cognitive function[40]. Mirtazapine and agomelatine also have low anticholinergic burdens[38], and are preferable in patients who are also anticoagulated. TCAs are highly anticholinergic and should be avoided. Note that anticholinesterase inhibitors can cause bradycardia, which may be compounded by antidepressants, increasing the risk of ventricular arrhythmia.

Recommendation: vortioxetine, or mirtazapine/agomelatine

2.8 Falls

There are several factors that may contribute to the risk of falls, and in any single patient falls may be multifactorial. Depression itself increases the risk of falling, and this may contribute to the observation that falls risk is highest in the first weeks of treatment with antidepressants[41]. Orthostatic hypotension, hyponatraemia, sedation and cardiac arrhythmia are also responsible for antidepressant-induced falls. TCAs are alpha blockers and increase the risk of orthostatic hypotension and are therefore not recommended. The MAOIs and trazodone are also associated with orthostatic hypotension[32]. Mirtazapine and agomelatine may aid sleep at night, but if a hangover effect persists then this may increase falls risk during the day.

SSRIs can be alerting, but if this contributes to nocturia and disturbed sleep then they may also indirectly cause daytime drowsiness[42]. SSRIs[43] can increase the risk of osteopaenia, and TCAs appear to increase fracture risk[44]. The risk of fracture is higher in a patient with frequent falls, and further increased by concurrent osteopaenia. It is thought that SSRIs mediate this by serotonergic effects on bone metabolism, so SNRIs are also implicated and drugs such as mirtazapine may be preferable, although data are limited[44]. No single antidepressant is clearly preferable here; choice should ideally be made considering the balance of individual factors for each patient.

Monitoring of sodium, especially in the first few weeks of treatment[17] and bone mineral density for those taking serotonergic antidepressants who are particularly vulnerable to osteoporosis or its consequences should be considered.

Recommendation: mirtazapine

2.9 Diabetes

SSRIs are first-choice antidepressants in diabetes[32]; sertraline, fluoxetine and escitalopram have been shown to improve glycaemic control. Mirtazapine is less favourable due to effects on weight and potential for worsening of $HbA1_C$ in the longer term[32]. SNRIs can be used and do not appear to affect glycaemic control[32], but be aware of the risks to blood pressure and QTc outlined in section 2.1. TCAs are associated with weight gain and hyperglycaemia[32] so should be avoided. Of the MAOIs, irreversible inhibitors (phenelzine) can cause hypoglycaemia and weight gain, but moclobemide is likely to be safe[32]. Agomelatine is weight neutral, and limited data suggest that it does not worsen glycaemic parameters[32].

For all drugs, monitoring of BMs at initiation, dose changes and discontinuation is recommended.

Recommendation: sertraline

2.10 Chronic kidney disease

Most antidepressants can be used in renal disease; detailed advice on dosing for individual drugs is given in the Maudsley Prescribing Guidelines in Psychiatry[45]. TCAs may be less desirable due to their anticholinergic effects worsening urinary retention. If electrolytes are unstable, avoiding drugs more likely to prolong the QTc interval (citalopram, escitalopram) is advisable. Sertraline is a reasonable choice, as is mirtazapine (start at lower doses in severe renal impairment).

Recommendation: most antidepressants can be used, dose with caution

3 Drug-drug interactions[46]

3.1 ACEI

ACEI can cause SIADH, and resultant hyponatraemia. All antidepressants have been associated with the development of hyponatraemia – the risk is highest in the first weeks of treatment[17]. Monitor sodium levels in the first month of antidepressant treatment, especially in patients with other risk factors for developing hyponatraemia.

3.2 Beta blockers

Sotalol has a high risk of prolonging the QTc interval. Combination with antidepressants, especially TCAs, citalopram and escitalopram, should be avoided. Duloxetine, fluoxetine and

paroxetine (and to a lesser extent, citalopram and escitalopram) inhibit CYP2D6, so may increase exposure to propranolol, metoprolol, carvedilol and nebivolol[29].

3.3 Sacubitril/valsartan

No interactions, but note that hallucinations, paranoia and sleep disturbance (in the context of psychotic events) are mentioned by the manufacturer.

3.4 Ivabradine

Ivabradine causes bradycardia, which may exacerbate QTc prolongation – caution should be taken when combining with antidepressants that prolong the QTc[29].

3.5 Digoxin

Isolated case reports and a single case control study suggest the possibility of increased plasma levels of digoxin with fluoxetine, fluvoxamine, paroxetine or sertraline[47], but this is disputed[29]. Clinically significant problems are highly unlikely.

3.6 Hydralazine

The manufacturer notes a risk of enhanced hypotensive effect when hydralazine is combined with TCAs.

3.7 Nitrates

Nitrates are known to cause postural hypotension, particularly if combined with alcohol - TCAs, MAOIs and trazodone may add to this risk. The antimuscarinic effects of TCAs may cause dry mouth, which might affect the dissolution of glyceryl trinitrate sublingual tablets[29]. Switching to a glyceryl trinitrate spray is a possible alternative.

3.8 Loop diuretics

Symptomatic hypotension caused by loop diuretics may be worsened by other drugs that cause hypotension (TCAs, MAOIs, trazodone).

There is a possible increased risk of hypokalaemia when loop diuretics are given with reboxetine. Additionally, loop diuretics are known to cause hypokalaemia, and this increases the risk of torsade de pointes. Caution is advised if this occurs when combining with drugs known to prolong the QTc interval (TCAs, citalopram, escitalopram)[29].

Patients taking diuretics may be at increased risk of developing hyponatraemia. This risk may be enhanced by concurrent use of other drugs that can cause hyponatraemia, including antidepressants[29]. Monitoring of sodium is advised, especially in the first 4 weeks of antidepressant treatment and in patients with additional risk factors for hyponatraemia.

3.9 SGLT2 inhibitors

The non-selective MAOIs isocarboxazid, phenelzine, iproniazid and tranylcypromine can reduce blood glucose levels, possibly due to direct action on the pancreas, increasing insulin release. This may be beneficial in patients with hyperglycaemia, but may also contribute to hypoglycaemia in patients taking oral antidiabetics.

4 Counselling

- Patients should remain at the heart of all treatment decisions and be fully involved in decisions regarding choice of antidepressant.

- Agree with the patient the symptoms of their depression they are aiming to treat with the antidepressant. Discuss how to measure treatment success/failure based on this.
- Patients can be reassured that for most people (two thirds), the symptoms of their depression are reduced, or entirely eliminated, with the first antidepressant they try.
- The greatest effect on symptoms is seen in the first one to two weeks of treatment. They will not need to suffer weeks waiting for relief from symptoms. If they have no symptom relief within a few weeks of treatment, their medication can be changed.
- It is recommended that most people continue to take their antidepressant for 6 – 9 months after their symptoms subside. Some people, especially those who have had repeated episodes of depression, should take treatment for at least two years, or possibly longer.
- Antidepressants are not addictive. Unlike addictive substances, people do not need to take increasing doses of antidepressants to get the same effect, and do not crave antidepressants. They may, however, cause some withdrawal symptoms for some people on stopping. These can be reduced or eliminated by stopping slowly.

4.1 Patient information sources

- Royal College of Psychiatrists: https://www.rcpsych.ac.uk/mental-health/problems-disorders/depression
- Mind https://www.mind.org.uk/information-support/types-of-mental-health-problems/depression/about-depression/
- South London and Maudsley patient information leaflets: https://www.slam.nhs.uk/patients-and-carers/medication
- British Heart Foundation: https://www.bhf.org.uk/informationsupport/heart-matters-magazine/wellbeing/mental-health

5 Contacts

Siobhan Gee, principal pharmacist for liaison psychiatry: 07773108081; Siobhan.Gee@slam.nhs.uk

Psychiatric Medicines Information: 0203 228 2317; pharmacy_staff_medicines_information@slam.nhs.uk

With many thanks to the Maudsley Charity for funding this work as part of the Integrating our Mental and Physical Healthcare Systems Project as part of the King's Health Partners Mind & Body Programme.

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