# Chapter 1

# Cardiac Disease



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## INTRODUCTION

The influence of psychiatric symptoms on the functioning of the heart was first described in 1628 by Sir William Harvey, the English physician who discovered the cardiac circulatory system. Since then, numerous studies have proven him correct, finding mental illness to be a significant predictor of cardiac mortality across the spectrum of cardiac diseases. Treatment of the mental illness is therefore vital not only for relief of psychiatric symptoms, but also for optimal treatment of the cardiac disease.

Few data are available to compare efficacy of drugs for mental illness within individual physical illnesses, such as heart failure or coronary heart disease, and even fewer for patients who have more than one concurrent physical illness. When extrapolating data from studies in patients without cardiac disease, it should be noted that populations studied in these trials are different (e.g. cardiac disease patients tend to be older than populations with general depression). Perhaps more importantly, the biological symptoms of mental illnesses that are measured by standard rating scales may not appear to improve on addition of psychiatric drugs because of the overlap of these physical symptoms with ongoing symptoms of the heart disease (e.g. fatigue, insomnia). Failure to demonstrate response to a drug on a rating scale is of little importance in clinical practice (symptoms are the target) but is relevant if trial data are used to make decisions about drug choice. Conversely, it is also possible that illnesses such as depression or anxiety – specifically in the context of heart disease – are biologically distinct from general depression. Consequently, drug treatments may not be effective for this reason.

## HEART FAILURE

### Depression and anxiety in heart failure

As many as one in five patients with heart failure suffer from depression, more than doubling the mortality risk and trebling the risk of non-compliance with medical treatment recommendations[1]. Clinically significant symptoms of anxiety are also commonly reported in patients with heart failure (30%)[2]. Symptoms of heart failure and those of anxiety may overlap, increasing the apparent prevalence. A clear link between anxiety and mortality in heart failure has not been fully established, but an increased risk is evident for patients with other cardiac disorders such as coronary artery disease[3]. Of course, depression and anxiety may co-exist, and together they increase the risk of both cardiac rehospitalisation and mortality in patients with heart failure[4].

There are several factors that may give rise to the link between depression and anxiety, and poor cardiac outcomes in heart failure. These include biological changes that occur in association with the mental health condition (inflammation, autonomic dysfunction, alterations in the ability of platelets to aggregate, and endothelial dysfunction[2]). Adherence to medicines for the treatment of the heart failure or comorbidities may be affected, as may maintenance of a healthy lifestyle (smoking cessation, diet, exercise).

There are few data relating to the efficacy of pharmacotherapy in depression specifically with comorbid heart failure. The most well-known studies are SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) and MOOD-HF (Mood and Mortality in Depressed Heart Failure patients). SADHART-CHF demonstrated safety (although not efficacy) of sertraline[5], and MOOD-HF[6] the same for escitalopram. There are no randomised trials examining the pharmacological treatment of anxiety in heart failure patients.

## Psychosis and bipolar disorder in heart failure

Patients with serious mental illness (SMI – schizophrenia, bipolar disorder, and severe depression) have a reduced life expectancy compared with the non-SMI population[7]. Cardiovascular disease is a significant contributor to this[8]. Lifestyle interventions are as important in this population as they are in the general population[9]. Antipsychotics and mood stabilisers (lithium and mood-stabilising antiepileptics) commonly cause weight gain, hyperglycaemia, and hyperlipidaemia. Despite this, patients who take them have an overall reduction in cardiac (and all-cause) mortality[10]. This may be a direct beneficial effect of reduction in psychiatric symptoms, improved adherence to healthy lifestyle choices, and/or better compliance with physical health treatments. Heart failure outcomes in patients who have SMI are therefore strongly linked to the outcome of their mental illness, making effective treatment of the psychiatric symptoms a priority. This is an important factor when weighing the risks and benefits of individual psychiatric medication choice. Medication that is perceived as safer in heart failure but less effective for the mental disorder may not actually be the optimal choice for overall cardiac outcomes[11].

## Antidepressants

In general, SSRIs are considered first-line antidepressants, and this is also true for patients with heart failure. Of the SSRIs, sertraline[12,13] is generally well tolerated and efficacious in non-heart failure populations[14]. 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)[5]. Escitalopram has also demonstrated safety (although not efficacy) in patients with heart failure[6], but is more often associated with QT prolongation[15] than sertraline (although this association is disputed[16]).

Other options carry some cautions. Mirtazapine is consistently shown to promote appetite, probably due to $\alpha_2$ receptor blockade and affinity for $H_1$, $D_1$, and $D_2$ receptors[17], and is therefore less desirable in conditions such as heart failure where excess weight can be detrimental to clinical outcomes. Citalopram may be more likely than other antidepressants to prolong the QT interval and is not recommended for use in uncompensated heart failure[18]. SNRIs (venlafaxine and duloxetine) are associated with dose-dependent increases in blood pressure[19] (see section on hypertension), and venlafaxine and fluoxetine may also cause prolonged QT, particularly in combination with ivabradine[20]. Tricyclic antidepressants (TCAs) are generally avoided in patients with cardiac disease due to their effects on cardiac contractility, their proarrhythmic effects (due to blockade of cardiac sodium and potassium channels), and their potential to worsen ischaemic heart disease.

Hyponatraemia is a risk with all antidepressants in the first month of treatment. Depending on the patient's risk profile, the diuretic dose may need to be adjusted. If hyponatraemia persists, the dose of sacubitril may need to be reduced or stopped. Mirtazapine and agomelatine may be less commonly associated with hyponatraemia (but are not completely without risk). Close monitoring of sodium levels is recommended, especially in the first few weeks of treatment[21] and if patients have additional risk factors for developing hyponatraemia.

**Recommendation:** sertraline.

## Antipsychotics

Most antipsychotics are associated to some degree with numerous cardiac adverse events, including prolonged QT interval, tachycardia and orthostatic hypotension. They can also (rarely) cause myocarditis and cardiomyopathy, which can lead to the development of heart failure. Pharmacovigilance studies suggest that myocarditis and cardiomyopathy may be particularly associated with chlorpromazine, fluphenazine, risperidone, and haloperidol (and clozapine; see below)[22]. Haloperidol, olanzapine, quetiapine, risperidone, and sulpiride have higher affinity than others for cardiac potassium channels and are associated with a higher risk of ventricular arrhythmia and sudden cardiac death[23]. Cariprazine, lurasidone, brexpiprazole, and lumateperone are considered safer choices in patients at risk of cardiac events, as they appear to exert minimal effects on the QT interval. They, along with 'typical' antipsychotics such as haloperidol, are also less likely than other 'atypical' drugs to cause weight gain and have adverse effects on blood lipids[24]. Olanzapine and clozapine are particularly problematic in this regard, and so may worsen the patient's cardiovascular risk factor profile.

Where patients develop symptomatic heart failure that is suspected to be caused by antipsychotic-induced cardiomyopathy, the offending drug should be changed to a different agent. For some patients this may be challenging if their psychiatric illness fails to respond to alternative antipsychotics. It has been suggested that a cut-off of 45% ejection fraction be used as a threshold for treatment cessation, extrapolating from guidelines for monitoring of cardiotoxic chemotherapies[25], but the exact level depends on the clinical scenario. After this point, studies indicate that the left ventricular function is less likely to recover[25]. Up to this threshold, effective antipsychotic treatments can be continued with 3-monthly monitoring of heart failure symptoms and NT-proBNP (a significant rise indicates raised cardiac filling pressures and should prompt an ECHO)[26].

For patients with pre-existing heart failure who require an antipsychotic, or need their current antipsychotic switched, choice of drug should primarily be focused on efficacy and tolerability. As described above, cariprazine, lurasidone, brexpiprazole, and lumateperone are preferable from a cardiac safety perspective. It is not known whether pre-existing heart failure predisposes to drug-induced cardiomyopathy, but it is the case that drug-induced cardiomyopathy worsens heart failure. For this reason, monitoring for any unexpected deterioration in cardiac function on commencing a new antipsychotic in someone with heart failure is recommended. Continued vigilance is required as antipsychotics may cause cardiomyopathy after many months of treatment, and this monitoring is best managed in a multidisciplinary setting involving both the psychiatry and cardiology teams.

**Recommendation:** cariprazine, lurasidone, brexpiprazole, lumateperone. Avoid olanzapine.

### *Clozapine*

Of the antipsychotics, clozapine is particularly associated with myocarditis and cardiomyopathy (although these are still rare events). Nonetheless, it is possible to start clozapine in patients with pre-existing heart failure or continue clozapine if heart

**Table 1.1** Antipsychotics in heart failure

| Event | | Action |
|---|---|---|
| Antipsychotic-induced cardiomyopathy with symptoms of heart failure | Antipsychotic is effective. | Continue treatment if ejection fraction > 45%.<br><br>Switch treatment if ejection fraction < 45%.<br><br>Monitor symptoms and NT-proBNP 3 monthly. |
| | Antipsychotic is ineffective. | Switch, ideally to cariprazine, lurasidone, brexpiprazole, or lumateperone. |
| Non-antipsychotic induced heart failure (new or pre-existing) | Antipsychotic is effective. | Continue treatment. |
| | Antipsychotic is ineffective. | Switch, ideally to cariprazine, lurasidone, brexpiprazole, or lumateperone. |
| Antipsychotic-induced cardiomyopathy with ejection fraction < 45%. Offending antipsychotic has been stopped but alternative agents are ineffective. | | Ensure optimisation of heart failure treatments before and during rechallenge. Ideally, wait until ejection fraction > 45%.<br><br>Restart antipsychotic using a slow dose titration.<br><br>Minimum weekly assessment of heart failure symptoms, HR, temp, trop, BNP, ECG[26] during dose titration (some authors suggest twice weekly troponin and CRP[28]).<br><br>ECHO on completion of dose titration or earlier if indicated by symptoms or blood tests. |

failure develops during treatment. In many cases this may be essential. Switching to a different antipsychotic when clozapine is indicated will almost inevitably result in psychiatric relapse. This can have dire consequences on the ability of the patient to comply with treatment for heart failure. Successful rechallenge with clozapine, even where cardiomyopathy is thought to be clozapine-induced, is achievable[27]. The enhanced risk of drug-induced cardiomyopathy with clozapine when compared with other antipsychotics means that monitoring cardiac function whilst establishing treatment is even more important. Use a slow titration of initial doses and monitor as described in Table 1.1.

## Mood stabilisers

Pharmacovigilance database studies have linked lithium to an increased risk of myocarditis and cardiomyopathy[22], and case reports describe various cardiac adverse effects, including sinus node dysfunction, premature ventricular beats, atrioventricular block, and T-wave depression. These risks must be balanced against the (probably

unparalleled) efficacy of lithium in bipolar disorder. Carbamazepine may be associated with hypotension, bradycardia, atrioventricular block, and possibly heart failure[29]. Heart failure has also been reported with valproate[30], and a Danish cohort study recently found an increased hazard ratio for mortality due to heart failure in elderly patients with epilepsy treated with valproate, compared with lamotrigine (or levetiracetam)[31]. The authors postulated that this association may be due to the effect on cardiac conduction by valproate blockade of voltage-gated sodium channels, and possibly upregulation of anabolism of angiotensin II[31]. Other antiseizure drugs do not share this effect on angiotensin and may be safer.

In 2021, a warning that lamotrigine exhibits class 1B antiarrhythmic activity was added to the FDA product label. To date, no other regulatory authority has done the same. The warning is based on unpublished *in vitro* studies demonstrating that lamotrigine inhibits cardiac sodium channels, and may therefore slow ventricular condition, inducing arrhythmia. A study in healthy patients failed to find any such ECG changes, but it is possible that people with structural heart disease or myocardial ischaemia are at higher risk. Consequently, the FDA recommends avoiding lamotrigine in people who have cardiac conduction disorders, ventricular arrhythmias, or cardiac disease (including heart failure). The risk may be higher in people with elevated heart rates or who are taking other sodium channel blockers[32].

**Recommendation:** no drug is without risk. Lamotrigine may be preferable.

## Others

**Pregabalin** can cause peripheral oedema, and case reports have been published reporting an associated with exacerbation of heart failure[29]. It should be used with caution, depending on the clinical scenario. **Promethazine** is a phenothiazine derivative and may prolong the QT interval, but the likelihood of progression to torsade de pointes appears to be low[33]. **Diphenhydramine** has been linked to QT prolongation in case reports, but in the context of congenital abnormalities[34] or overdose[35].

**Benzodiazepines** may worsen outcomes in heart failure. In two studies examining the management of insomnia[36] or anxiety[37] in heart failure, use of benzodiazepines was associated with increased rehospitalisation for heart failure and cardiovascular death. It is possible that this is a result of reduced respiratory drive adversely affecting heart failure symptoms. Conversely, a cohort study with an average 8-year follow-up period found a reduction in mortality for patients with heart failure prescribed benzodiazepines[38], perhaps reflecting the impact of improved management of mental health on heart failure outcomes. This is echoed by a multicentre Spanish study[39], where use of benzodiazepines during acute exacerbations of heart failure was not associated with differences in mortality after 7 days, despite patients receiving benzodiazepines having more severe cardiac symptoms at baseline. The dose may be important. A large Taiwanese study[40] found a reduction in cardiovascular mortality and hospitalisation for heart failure in patients receiving benzodiazepines post myocardial infarction, but only where small doses were used (up to 5mg diazepam, or equivalent). This benefit was lost at higher doses, possibly due to confounding by disease severity (higher doses implying higher levels of anxiety), or interference with cardiac rehabilitation.

Overall, it is clear that treatment of anxiety is important for cardiac outcomes, and benzodiazepines may be useful but should ideally be reserved for short-term use, in line with more general guidance on management of anxiety disorders.

The **cholinesterase inhibitors** (donepezil, rivastigmine, galantamine) can have vagotonic effects on the heart rate (i.e. bradycardia), and some cases of QT interval prolongation have been reported. These events are uncommon[41], and several studies show a protective effect of cholinesterase inhibitors on new-onset heart failure[42] or heart failure hospitalisation[43]. **Memantine** also appears to be safe in heart failure and may reduce hospitalisation[44].

## CORONARY HEART DISEASE

### Depression and anxiety in coronary heart disease

Between 15% and 30% of patients with coronary heart disease (CHD) are diagnosed with depression, a prevalence two to three times higher than the general population[45], and experts consider this to be an underestimation. Depression is a risk factor not only for the development of CHD but for cardiovascular morbidity and mortality in patients with established CHD[46]. Numerous mechanisms have been proposed to explain this relationship[47], both biological (altered autonomic nervous system activity, increased catecholamine levels, increased inflammatory activity, endothelial dysfunction, and platelet dysfunction) and behavioural (sedentary behaviour, poor diet, smoking, low medication adherence). There are now several studies examining whether treating depression can improve outcomes in CHD. The largest of these, ENRICHD[48], failed to find any reduction in cardiac events when sertraline was given to patients who had had a myocardial infarction. However, secondary analysis of this and other trials, including SADHART[49,50] and MIND-IT[51], suggests that improvement in depression may positively affect overall survival in patients with CHD.

Similarly, anxiety symptoms are common in CHD[52]. Anxiety is also an independent risk factor for the development of CHD[53], and for cardiac[54] and all-cause mortality[55] in CHD, particularly when comorbid with depression[55]. Despite this, there are very few studies specifically examining treatment of anxiety disorders as a primary outcome. Where they do exist, only generalised anxiety disorder or health-related anxiety are assessed (e.g. anxiety specifically around a cardiac intervention)[56]. Of note, anxiety disorders may share common symptoms with CHD, including tachycardia, shortness of breath, and chest pain.

### Psychosis and bipolar disorder in coronary heart disease

A very large meta-analysis that included more than 3 million patients with serious mental illness and over 100 million controls[8] confirmed an increased risk of CHD for people with schizophrenia. There was no significant association between CHD and bipolar disorder in this analysis, but bipolar disorder has been significantly associated with cardiovascular disease in longitudinal studies, and with cardiovascular-related death[8].

Some data suggest that of the SMI subtypes, bipolar disorder confers the highest 10-year cardiovascular risk[57]. Various contributing factors are proposed, including accelerated atherosclerosis, endothelial dysfunction, and oxidative stress[58]. Despite the increased risk, patients with SMI are less likely to receive evidence-based management of CHD, both in terms of diagnosis and treatment[58].

## Antidepressants

TCAs should be avoided in patients with CHD. Studies demonstrate negative cardiac outcomes for patients with CHD taking TCAs (increased heart rate, reduction in heart rate variability, and increased pulse[59,60]). The safety of SSRIs and mirtazapine post myocardial infarction (MI) has been demonstrated in several landmark studies[5,48,61], and it has further been suggested that the inhibitory effect of SSRIs on platelet activation may actually protect against MI[62]. This potential benefit (studies thus far have been underpowered to confirm this claim[5]) must be balanced against the increased risk of bleeding and gastric ulceration[63] 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. See section on anticoagulation.

**Recommendation:** sertraline, or mirtazapine if significant bleeding risk.

## Antipsychotics

Whether antipsychotics increase the risk of CHD is not clear. Some meta-analyses suggest an increased risk of MI for antipsychotic drug users[64,65], others do not[66,67]. The heterogeneity and retrospective design of many of the published studies (making it difficult to control for confounding factors) may be contributing to the variation in results. When considering individual antipsychotic drug choice, several factors may be relevant. These include the likelihood of the antipsychotic to cause ventricular arrhythmia (a cause of sudden cardiac death), or to prolong the QT interval (increasing the risk of torsades de pointes, leading to sudden cardiac death). The effect of the antipsychotic on metabolic parameters is also important, as cholesterol and triglyceride concentrations, hypertension, and obesity are associated with increased risk of CHD[68]. One study suggested that $D_3$ receptor antagonism may contribute to the development of MI, possibly because of effects on platelet aggregation, atherosclerosis, vascular remodelling, and intimal permeability[69]. The authors linked this to their observation that amisulpride, a drug with particularly high affinity for the $D_3$ receptor, also had the highest risk of MI in their study. This finding requires replication.

Antipsychotics with no apparent effect on the QT interval are cariprazine, brexpiprazole, lurasidone, and lumateperone[12], and these drugs also have more benign metabolic profiles than others[24]. They are therefore preferred in patients with CHD. Aripiprazole may be used if a depot is required (note that there is a possible association with QT interval prolongation[12]).

**Recommendation:** cariprazine, lurasidone, brexpiprazole, or lumateperone.

## Mood stabilisers

Lithium can be used in CHD, with some data suggesting it may even slow the progression of atherosclerosis[70] and reduce cardiovascular mortality[71]. It can cause ECG changes, but at therapeutic plasma concentrations these are usually clinically insignificant[72] (but note that the manufacturers contraindicate lithium use in cardiac disorders with rhythm changes). Carbamazepine is an inducer of the hepatic cytochrome P450 enzyme system, which is involved in the synthesis of cholesterol. As a result, carbamazepine increases serum cholesterol[73,74] and this may translate to an increased risk of MI[75]. Lamotrigine and valproate do not negatively affect cholesterol concentrations[73]. Valproate is particularly associated with weight gain[73] but several studies show that use is associated with lower cholesterol concentrations, and possibly a corresponding reduction in the incidence of MI[75–77].

**Recommendation:** lithium, lamotrigine, or valproate (but monitor for metabolic syndrome).

## Others

**Pregabalin** can cause significant weight gain but, similarly to valproate, does not seem to cause clinically significant changes in cholesterol[78] or increase the risk of MI[75]. Most studies examining these clinical outcomes are conducted in people with epilepsy, which itself may be a risk factor for cardiovascular events[79]. Where studies do control for the indication for the antiepileptic drug, however, the associations appear to remain[75].

The manufacturers of **promethazine** advise caution in patients with severe coronary artery disease, but the exact reason for this is not clear. As described above, promethazine may prolong the QT interval, but its torsadogenic potential is low[33]. Similarly, the use of **diphenhydramine** is cautioned by the manufacturers in cardiovascular disease, presumably due to effects on QT interval. Otherwise, antihistamines appear to be safe. **Benzodiazepines** are used in the management of acute coronary syndrome, and limited data suggest they improve cardiac mortality risk post MI when used in low or moderate doses[40]. This may be a result of better management of anxiety, rather than a direct effect of the drugs themselves. Higher doses have been associated with increased cardiac mortality[80].

As described above, the **cholinesterase inhibitors** may prolong the QT interval, so caution is advised in patients who are newly post MI. Otherwise, along with **memantine**, they may be protective for cardiovascular outcomes in coronary heart disease[81], possibly due to a reduction in myocardial revascularisation[43,82,83]. For older adults, particularly those at risk of a cardiac event, the importance of minimising the total anticholinergic burden of prescribed medication is becoming increasingly clear. A recent case-case-time-control study found an association between anticholinergic burden and acute cardiovascular events, with greater burdens conferring higher risk[84]. Use a tool such as Medichec (medichec.com) to calculate anticholinergic burden and deprescribe or select drugs with a lower score where possible.

## HYPERTENSION

### Depression and anxiety in hypertension

A relationship between hypertension and depression has been discussed since as early as 1898, when blood pressure was noted to rise in patients with depression[85]. Since then, research has suggested that the relationship may be bidirectional. Depression is an independent risk factor for developing hypertension[86], and the 'vascular depression' hypothesis proposes that cerebrovascular disease, for which hypertension is a risk factor, causes microvascular brain damage that may drive some depressive symptoms[87]. In contrast, studies in healthy populations show higher systolic blood pressure to be linked to a better mood and increased well-being[88]. Recently, a large UK imaging study with a 10-year follow-up time confirmed these two apparently contradictory associations – higher systolic blood pressure is linked to fewer depressive symptoms, and a diagnosis of hypertension is associated with more depressive symptoms[89]. The authors suggest that there may be a shared mechanism between subjective experience, emotional processing and pain that involves regulatory baroreceptors.

Anxiety was predictive of incidence of hypertension in the Framingham Heart Study[90], a finding also demonstrated in earlier studies[91] and confirmed in meta-analyses[92]. Further, patients with hypertension may be at heightened risk of developing anxiety, possibly a result of fear of the diagnosis[93]. It may be that sympathetic nervous system hyperactivity and cardiovascular oxidative stress contribute to the relationship[94].

### Psychosis and bipolar disorder in hypertension

Meta-analysis suggests a prevalence for hypertension in schizophrenia of 39%[95], but rates may be higher in some areas (58% in the USA[48], 54% in England[96]). A higher risk of hypertension is also found in bipolar disorder[97,98], and in both conditions, treatment of hypertension is poor[98]. The presence of metabolic disorder is clearly important, and antipsychotics add to this risk. Other factors may also be influential; a genetic link between cardiometabolic disease and bipolar disorder is suggested[99], and inflammation and autonomic activity in psychosis may also be contributory[100].

### Antidepressants

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[101]. 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[102]

(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[103]). The anticholinergic effects of drugs such as TCAs may also contribute to increases in systolic blood pressure[102]. None is recommended for patients with pre-existing hypertension.

SSRIs do not appear to affect blood pressure[104] and are therefore preferable.

**Recommendation:** sertraline.

### Antipsychotics

Antipsychotics may cause hypertension either acutely, via $\alpha_2$ adrenergic receptor antagonism, or chronically, due to weight gain. Olanzapine, risperidone, and particularly clozapine have higher affinity for $\alpha_2$-adrenergic receptors than other antipsychotics[12], making sharp rises in blood pressure on initiation of these drugs more likely, due to noradrenaline-mediated vasoconstriction. Olanzapine and clozapine are associated with more weight gain than other antipsychotics[24], which increases the risk of developing (or worsening) hypertension.

**Recommendation:** avoid olanzapine and risperidone.

### Mood stabilisers

Hypertension has been rarely described in case reports with carbamazepine[105] and valproate[106,107], although causality is not certain. Lithium[108] and lamotrigine are not associated with hypertension.

**Recommendation:** all mood stabilisers are likely to be safe.

### Others

**Pregabalin** and **promethazine**[109] are not associated with hypertension. The manufacturers of **diphenhydramine** caution against its use in hypertension when given parenterally, as large intravenous doses produce a strongly anticholinergic effect[110], but this does not appear to be a significant problem when taken orally. **Benzodiazepines** have hypotensive effects[111], possibly due to potentiation of the inhibitory effect of GABA and vasodilation[112]. Of the **anticholinesterase inhibitors,** rivastigmine has been rarely associated with hypertension in post-marketing surveillance, and hypertension is commonly reported as an adverse effect with galantamine. Donepezil does not appear to cause problems with blood pressure. Hypertension is common with **memantine** (4.1% of patients compared with 2.8% taking placebo[113]).

## STROKE

### Depression, anxiety, and stroke

Post-stroke depression is common, with a third of stroke survivors developing depression at some point after the event[114]. The frequency is highest in the first year, affecting

one in three patients[115]. The South London Stroke Register found the cumulative incidence to be 55%[116], positioning post-stroke depression as the norm rather than the exception. Various reasons for this have been postulated, including (1) depression being a risk factor for stroke; (2) both depression and stroke having risk factors in common; (3) depression being a psychological reaction to stroke; (4) depression being secondary to other stroke outcomes, such as cognitive impairment; and (5) stroke having a direct pathophysiological effect on the brain[116]. Post-stroke mood disorders are strictly defined by the Diagnostic and Statistical Manual 5 (DSM-5) as mood disorders *due to* stroke, but the ability to definitively determine causality in clinical practice is lacking. Trials generally include symptoms of depression appearing at any time point post-stroke and include patients who had pre-existing depression diagnoses. The most consistent predictors of post-stroke depression are physical disability, stroke severity, a history of depression, and cognitive impairment[115]. It is associated with poorer functional outcomes after stroke[115].

Anxiety is also common post-stroke, with about one in four patients affected[117]. Comorbid depression is common[118]. Evidence to support optimal treatment choice is sparse[119], despite an association of severe post-stroke anxiety with poor outcomes and quality of life[120].

## Psychosis, bipolar disorder, and stroke

Schizophrenia[8,121] and bipolar disorder[8,122,123] are associated with an increased risk of stroke, with SMI as a whole conferring a two-fold increased risk[122]. This is likely to be a result of the increased cardiovascular comorbidity in SMI, including diabetes, hypertension, and hyperlipidaemia. Not only is there an increased likelihood of stroke but there is also increased mortality post-stroke in both the short (30-day) and long (5-year) term[122,124]. This may be a consequence suboptimal clinical care. Studies done in various countries worldwide have shown that patients with schizophrenia are less likely to receive thrombolysis or carotid imaging, be screened for hyperlipidaemia, be prescribed antihypertensives or anticoagulants, achieve target lipid levels post-stroke, or receive outpatient stroke care[125–129]. In one study, this translated to mortality at 1-year post-stroke in patients over 70 years of 47%, compared with 35% for those without schizophrenia[126].

## Antidepressants

SSRIs and nortriptyline are widely recommended as the antidepressants of choice post-stroke[12]. They may be associated with less dependence on carers post-stroke, less disability, less neurological impairment, and less anxiety and depression, including in people without a diagnosis of depression[130]. Treatment with fluoxetine or nortriptyline has been shown to reduce long-term mortality in comparison with placebo, including in patients who were not depressed at baseline[131]. This protective effect appears to remain even if antidepressants are only given for a short period following the stroke, suggesting that the mortality risk exceeds the duration of the depression[131]. SSRIs, however, are problematic to use in patients also taking anticoagulants (inevitable if the stroke was

ischaemic) or at risk of bleeding for other reasons (those who suffered haemorrhagic stroke). Nortriptyline is more attractive in this regard. Mirtazapine and agomelatine largely avoid issues with bleeding, but data supporting use post-stroke are entirely lacking for agomelatine and are 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[132]. Other studies support the safety and efficacy of mirtazapine post-stroke[133,134].

**Recommendation:** nortriptyline or mirtazapine if bleeding is a concern, but monitor for weight gain with mirtazapine. Otherwise, SSRI.

## Antipsychotics

The association of antipsychotics with a heightened risk of stroke in elderly patients with dementia is well described. What this means for younger patients without dementia, who are taking antipsychotics for other mental illnesses, is less clear. Few studies specifically address this question, and where they do exist they use heterogeneous outcomes (stroke incidence versus mortality from stroke, for example) and durations of follow-up (weeks to years). The impact of changes in antipsychotic prescription type is not clearly accounted for, and confounding by indication is difficult to control. Where studies attempt to report risk of stroke by drug type, this is usually by 'first-generation' versus 'second-generation' drugs, and results are conflicting.

Some studies report different results depending on stroke type (one Taiwanese study found an increased risk of ischaemic stroke, but not haemorrhagic, with atypical drugs)[135]; others do not report the stroke subtypes separately[136]. Systematic review and meta-analyses also draw different conclusions depending on their chosen inclusion criteria[67,136]. Overall, it seems possible that antipsychotics may increase the risk of stroke. Whether this is due to some direct, acutely mediated effect is not clear. It is certainly the case that antipsychotics increase the risk of obesity and insulin resistance, which in turn are risk factors for cardiovascular and cerebrovascular disease. They are also associated with an increased risk of venous thromboembolism. At the moment, there are insufficient data to support choosing one drug over another, but minimising weight gain is important.

**Recommendation:** no obvious optimal choice. Avoid weight gain.

## Mood stabilisers

Animal models show a neuroprotective effect of lithium post-stroke[137], and a few small trials suggest this benefit may translate into humans[138], although data are as yet very limited[139]. In terms of *de novo* stroke, lithium appears to confer either no extra risk[140], or possibly a reduced risk[141]. Variation in the histone deacetylase 9 gene (HDAC9) has been identified as a cause of large artery stroke. Inhibiting the activity of the HDAC9 protein might therefore reduce the risk of stroke, and one drug that has this activity is sodium valproate. Data so far available suggest that this might be the case[77,142] (but note one case-crossover study finding an increased risk of haemorrhagic stroke with acute

use of valproate in bipolar disorder[140]). Lamotrigine appears to be safe[140,143]. Carbamazepine is associated with a higher risk of stroke than the other mood-stabilising antiepileptics[77,140] and should be avoided.

**Recommendation:** lithium, valproate, lamotrigine.

### Others

**Pregabalin** is widely used in the treatment of pain post-stroke[144], and as with lithium, animal studies suggest a role in brain recovery[145]. Similarly, **promethazine** may be anti-inflammatory post-stroke[146]. **Diphenhydramine** is not known to pose a problem in stroke.

Animal models show a neuroprotective effect for GABA receptor agonists such as **benzodiazepines** in cerebrovascular disease, but this does not appear to extend to improvement in outcomes for acute stroke in people[147]. Benzodiazepine use may in fact increase mortality post-stroke[148], and there may be a dose-related increased risk of incident stroke[149]. This may be due in part to an increased risk of pneumonia for patients taking benzodiazepines[150], oversedation increasing the need for intubation, or higher incidence of falls. However, there are many confounding factors, including the increased likelihood of benzodiazepine use, particularly in patients who have other predictors of mortality such as delirium, agitation, or anxiety post-stroke, and so a direct causal association has been disputed[151]. Nonetheless, it is prudent to avoid use where possible and to minimise doses where not possible.

**Acetylcholinesterase inhibitors** may be protective for ischaemic stroke, possibly because of a protective effect on endothelial cells and anti-inflammatory mediated reduction in atherosclerosis[152]. They may also improve cognitive and functional impairment post-stroke[153,154]. **Memantine** may exert similar neuroprotective effects from stroke by inhibition of NMDA channels, reducing excitotoxic injury[155]. Not all studies examining the safety of acetylcholinesterase inhibitors control for concurrent use of antipsychotics, which are known to increase the risk of stroke in dementia. Other confounders are also important, including BMI and physical activity, hypertension, and smoking. These discrepancies in study design may explain the findings by some of an increased stroke risk in previous users of acetylcholinesterase inhibitors[156]. However, the consensus is that they, and memantine, are likely to be safe.

## ATRIAL FIBRILLATION

### Depression, anxiety, and atrial fibrillation

Depression increases the risk of developing atrial fibrillation[157,158], and the prevalence of depression is higher in patients with atrial fibrillation than in the general population (8–38% vs 1–2%)[157]. The reasons for this may be similar to those for other cardiac conditions, including inflammation, oxidative stress, autonomic nerve function, hypothalamic-pituitary-adrenal axis imbalance, and the burden of cardiac symptoms on quality of life[159]. This association extends to an increased risk of recurrence of atrial

fibrillation after catheter ablation in patients with depression[160]. As with other cardiac conditions, depression is also associated with increased cardiovascular mortality in atrial fibrillation[161]. Depression and atrial fibrillation are both associated with non-adherence to cardiac treatment regimens[162], and this may contribute to the increase in mortality risk[163].

Chronic stress and anxiety may increase the risk of atrial fibrillation in the same way as for depression, through inflammation, oxidative stress, and increased sympathetic activity resulting in catecholamine overload[164]. Anxiety is a risk factor for mortality in patients with coronary heart disease and atrial fibrillation[165].

## Psychosis, bipolar disorder, and atrial fibrillation

Patients with schizophrenia and bipolar disorder have a higher likelihood of developing atrial fibrillation, with one study finding a two-fold higher risk[166]. Data are emerging to suggest a possible genetic link with schizophrenia[167]. Schizophrenia is associated with a poorer prognosis in atrial fibrillation, and Danish authors have shown that this may be linked to disparities in the quality of care for the cardiac condition. Patients with mental health conditions – including depression, bipolar disorder, anxiety, and schizophrenia – are less likely to receive antiarrhythmic therapy[168] or oral anticoagulation[163,169,170], and less likely to adhere to anticoagulation in the long term[171].

Risk factors for cardiovascular disease and mortality are common in serious mental illness and also play a part in the increased risk for ischaemic stroke, thromboembolic events, and major bleeding in patients with schizophrenia or bipolar disorder and atrial fibrillation[172].

## Antidepressants

Serotonin promotes intracellular calcium overload, which is potentially arrhythmogenic[173]. Preclinical and clinical data show that stimulation of 5-$HT_4$ receptors can trigger sinus tachycardia and atrial arrhythmias[174]. Whether serotonergic antidepressants increase the risk of incident atrial fibrillation in practice is not entirely clear in the published literature. Given the known impact of depression on the risk of atrial fibrillation, there is a clear potential for confounding by indication, which is not always accounted for in meta-analyses on the subject[175]. This is demonstrated by a large Danish study, which found a three-fold higher risk of atrial fibrillation immediately before and after starting antidepressants, but the association gradually attenuated over the following year[176]. This suggests that treatment of depression may reduce the longer-term risk of developing atrial fibrillation. Other studies also find that antidepressants are not associated with atrial fibrillation[173], but some cast doubt on this conclusion[177,178]. More studies are needed that are specifically designed to look at whether possible proarrhythmic properties of antidepressants oppose the antiarrhythmic benefits of improving depressive symptoms.

TCAs should be avoided in patients with cardiac disease, as discussed earlier in this chapter. Their effects on slowing of intraventricular conduction mean that they are

generally contraindicated in disorders of cardiac rhythm[179]. Mirtazapine and agomelatine appear to be safe choices in relation to cardiac conduction.

Other than an effect on the risk of atrial fibrillation itself, the obvious problem with antidepressants is that of bleeding risk. Stasis of blood in the atria during fibrillation predisposes to clot formation and substantially increases the risk of stroke, so anticoagulation is essential. See section on anticoagulation for more detail surrounding drug choice.

The ideal choice of antidepressant in atrial fibrillation is therefore one that strikes a favourable balance between risk to cardiac conduction and risk of additive bleeding with concurrent anticoagulants. Mirtazapine and agomelatine are the least likely to cause problems in either regard (although mirtazapine is not entirely without bleeding risk; see anticoagulation section). TCAs are less likely to cause bleeding problems than SSRIs but are probably less safe in cardiac disease.

**Recommendation:** mirtazapine or agomelatine. SSRIs can be used, but beware of the interaction with warfarin and other anticoagulants.

## Antipsychotics

Atrial fibrillation is described in case reports to be associated with aripiprazole[180,181], clozapine[182,183], olanzapine[182,184] and paliperidone[185], and a nested case control study found current antipsychotic use to be associated with a 17% increased risk of atrial fibrillation relative to non-users[186]. The reason for this apparent association is not clear, but cardiovascular comorbidities such as hypertension, diabetes, and coronary heart disease are very likely play a part. Other proposed mechanisms include effects on the autonomic nervous system, cardiac muscarinic blockage[186], and stimulation of the hypothalamic-pituitary-adrenal axis[187]. There is evidence that compared with controls, patients with schizophrenia are more likely to have an increased heart rate, QTc prolongation, and pathological Q waves. In one study, patients taking any antipsychotic, especially clozapine or multiple concurrent antipsychotics, were particularly likely to have an abnormal ECG (predominantly QTc prolongation, right or left conduction disturbances, or pathological Q waves)[188]. Aripiprazole was the only antipsychotic not implicated in this effect. Interestingly, this study found no association between atrial fibrillation and antipsychotics (or schizophrenia).

**Recommendation:** cariprazine, brexpiprazole, lurasidone, lumateperone. Aripiprazole may also be used but is not entirely without effect on the QT interval.

## Mood stabilisers

Valproate does not appear to be associated with atrial fibrillation, other than a single case report of atrioventricular conduction block[189]. Carbamazepine and lamotrigine are not associated with atrial fibrillation. Lithium also seems safe but ECG changes, including atrial fibrillation, are known to occur in acute and chronic intoxication[190]. Ensuring plasma concentrations are kept within therapeutic ranges is therefore even more important in a patient with pre-existing atrial fibrillation.

**Recommendation:** all options are safe.

## Others

Two case reports implicate **pregabalin** in the development of atrial fibrillation, although both were patients hospitalised for infections[191,192]. One study in elderly patients found a dose-related increased incidence of initiation of antiarrhythmic drugs and anticoagulants in patients in the 3 months after starting pregabalin (or gabapentin)[193]. This finding has yet to be replicated but should perhaps prompt extra caution (cardiac monitoring for 3 months) in elderly patients.

**Promethazine** was associated with a higher risk of hospitalisation for atrial fibrillation in elderly patients than loratadine or betahistine in one study conducted in Denmark[194]. The risk was higher in patients with prior cardiac arrhythmias, heart failure, or those on other arrhythmogenic drugs. The authors postulate that this may be due to prolongation of the QT interval, which is known to predispose to atrial fibrillation[195]. As discussed earlier in this chapter, other authors have found that although promethazine is associated with QT interval prolongation, it is at a subclinical level that is not torsadogenic[33]. Of note, the Danish study found no association between promethazine use and myocardial infarction. The authors hypothesise that the association between promethazine and atrial fibrillation in their study was the result of subclinical QT interval prolongation adding arrhythmogenic potential to patients already at risk due to their age and history of cardiac disease.

There are no other published reports of an association between promethazine and atrial fibrillation and given the widespread use of the drug it seems likely that at most, this must be a rare event. Promethazine (and other anticholinergic drugs) should be avoided where possible in elderly patients due to negative effects on cognition, sedation, and falls[196]. The dramatic increase in risk of atrial fibrillation found in this study adds to these concerns, particularly in elderly patients with a history of cardiac disease, but requires replication. **Diphenhydramine** is not associated with atrial fibrillation.

A recent, large Taiwanese cohort study found an increased incidence of atrial fibrillation in patients taking hypnotics, including **benzodiazepines**[197]. The effect was dose-related. The reason for this association may be confounding by indication (hypnotics are more likely to be prescribed to people with psychiatric disorders, which themselves are risk factors for atrial fibrillation), or observation bias (people taking hypnotics are more likely to visit a clinician and have a routine ECG that then identifies asymptomatic atrial fibrillation). A further possibility is a direct effect of GABA-mediated inhibition of the sympathetic and parasympathetic nervous system having a detrimental effect on cardiac autonomic function. Whatever the cause of the association, it is clearly wise to minimise the use of benzodiazepines in all patients, including those with cardiac disease. There is also an increased risk of falls in elderly patients with atrial fibrillation[198], which is increased further in patients who take benzodiazepines[199].

The **acetylcholinesterase inhibitors** are known to cause bradycardia, which may be problematic in patients with supraventricular cardiac conduction conditions such as paroxysmal atrial fibrillation. Otherwise, ECG changes or arrhythmias are rare[200,201]. Donepezil may be more associated with QT prolongation than rivastigmine or galantamine, but the evidence for this is inconclusive and limited to case reports, and the potential mechanism for any differences between the drugs is unclear[201]. **Memantine** is

not associated with cardiac arrhythmia. Preclinical models suggest it may even be able to prevent and terminate atrial fibrillation[202].

## ANTICOAGULATION

### Antidepressants

Serotonergic antidepressants are associated with an increased risk of bleeding and of a prolonged duration or severity 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 (warfarin or non-vitamin K antagonists), who are at increased risk of bleeding if also given a serotonergic antidepressant[203,204].

Options include trazodone, mianserin, reboxetine, dosulepin, moclobemide, nortriptyline, phenelzine, trimipramine, lofepramine, mirtazapine and agomelatine. Trazodone and mianserin are recommended by the UK National Institute for Health and Care Excellence (NICE)[13], but trazodone may increase digoxin levels[205]. Reboxetine is not effective and there is a risk of hypokalaemia and hypocalcaemia when it is given with diuretics[205]. TCAs are proarrhythmic and TCAs and MAOIs are associated with increased blood pressure. Mirtazapine and agomelatine are probably safer alternatives, although note the risk of weight gain with mirtazapine. A small study in healthy subjects showed a minor increase in the INR when mirtazapine was combined with warfarin[206] (the mean increased from 1.6 to 1.8). This was not considered clinically significant, but two case reports describe much larger increases in INR[207,208]. Monitor INR if mirtazapine is added to warfarin, at initiation and at dose changes. There is also evidence of an increased bleeding risk when mirtazapine is combined with non-vitamin K antagonist oral anticoagulants (NOACs)[209].

**Recommendation:** mirtazapine or agomelatine.

### Antipsychotics

Analogous to serotonergic antidepressants, antipsychotics that are antagonists at the $5\text{-HT}_{2A}$ receptor may also affect platelet aggregation, and therefore theoretically contribute to an increased risk of prolonged bleeding. A single case-control study suggested an increased risk of gastrointestinal and intracranial bleeding for patients taking antipsychotics[210], but did not find an association between the degree of affinity with the $5\text{-HT}_{2A}$ receptor, and has yet to be replicated.

There is a further issue to consider where patients are taking NOACs. NOACs are substrates of P-glycoprotein, metabolised by CYP3A4. Antipsychotics that are CYP3A4 and/or P-glycoprotein inhibitors may therefore increase the plasma concentration of NOACs, enhancing their anticoagulant effect and increasing the risk of prolonged bleeding. Drugs such as haloperidol and quetiapine, which are mainly metabolised by CYP3A4 and also inhibit P-glycoprotein, may be more likely to cause major bleeding events than antipsychotics

such as olanzapine, where CYP3A4 plays a more minor role in metabolism[211]. However, specific evidence for an interaction effect between antipsychotics and NOACs is limited. Pharmacokinetic studies that examine NOAC plasma concentrations in combination with other drugs show that significant interaction effects occur mainly with substances that strongly inhibit both the CYP3A4 and P-glycoprotein pathways. The clinical effect for antipsychotics is therefore likely to be minimal. One large Taiwanese cohort study found an increased risk of bleeding when patients with atrial fibrillation were exposed to a NOAC and an antipsychotic, with the highest risk seen in patients taking haloperidol[211].

When using antipsychotics for behavioural symptoms in dementia or delirium in elderly patients, and especially if there is concurrent renal impairment (which also increases NOAC plasma concentrations), consider avoiding haloperidol and quetiapine and choose olanzapine or aripiprazole (drugs less associated with a higher risk of bleeding in the cohort study). Otherwise, there is currently no evidence to strongly support changing standard practice.

In contrast to the foregoing, antipsychotics are also associated with an increased risk of venous thromboembolism, particularly at the start of treatment[212]. This may be relevant if considering treatment options in patients who have already experienced a thromboembolic event and may be at risk of another, and particularly if antipsychotics are not definitively indicated in such patients (that is, another drug or non-drug measure could be used). The absolute risk is small – in a large, UK-based case-control study, there were an extra four cases of venous thromboembolism per 10,000 patients treated over 1 year across all age groups, and 10 for patients aged 65 and over[212].

**Recommendation:** all antipsychotics are associated with a small risk of thromboembolism. Avoid haloperidol and quetiapine in patients taking NOACs.

## Mood stabilisers

Sodium valproate causes a variety of haematological abnormalities, including inhibition of platelet aggregation and thrombocytopenia[213], but the clinical significance of this is disputed. Some retrospective studies demonstrate an increase in perioperative bleeding, others do not[214]. Most of the published data are in children undergoing neurosurgery for epilepsy. How this should be interpreted for adults taking valproate for mental health disorders is unclear – children appear to be more at risk of valproate-induced coagulopathies than adults[215]. Retrospective studies have found an association between heavy menstrual bleeding and valproate in women with serious mental illness[216]. Descriptions of severe (or even fatal) haemorrhage in adult patients are limited to case reports (again, in epilepsy)[217–219]. Thrombocytopenia and bleeding are reported at both supratherapeutic and subtherapeutic plasma concentrations. Valproate is an inducer of CYP3A4 and P-glycoprotein, which may result in lower plasma concentrations of NOACs. This has led to the combination being contraindicated by the European Society of Cardiology[220], although evidence of the interaction in clinical practice is limited[221,222].

Carbamazepine is a potent CYP3A4 and P-glycoprotein inducer, and therefore increases the metabolism of both vitamin K antagonists and NOACs. This is clinically

important, resulting in increased incidence of thrombotic events[223,224]. Consider also the risk of overcoagulation if carbamazepine is stopped in a patient taking an anticoagulant, if doses have been adjusted during co-treatment to account for the interaction. Lamotrigine does not interact with anticoagulants or increase the risk of bleeding. Lithium is also free of anticoagulant drug interactions, and not associated with an increased risk of bleeding (in fact, preclinical studies suggest it may be neuroprotective after intracranial haemorrhage[225]).

**Recommendation:** lithium, lamotrigine.

### Others

As for lithium, **pregabalin** does not interact with anticoagulants, is not associated with an increased risk of bleeding, and is suggested in preclinical studies to be neuroprotective after intracranial haemorrhage[226]. **Promethazine**, **diphenhydramine**, and **benzodiazepines** are not known to cause problems with bleeding or anticoagulation.

Case reports have suggested a link between **acetylcholinesterase inhibitors** and bleeding events[227–229]. This may be due to inhibition of platelet activation, as acetylcholine is thought to be an endogenous inhibitor of platelets[230]. Limited data from cohort and case-control studies do not seem to support this theory, with several studies failing to find an association with bleeding events and acetylcholinesterase inhibitors[156,231]. **Memantine** is not associated with an increased risk of bleeds.

## ADHD MEDICATION IN ADULTS WITH CARDIAC DISEASE

The stimulant drugs methylphenidate and dexamphetamine, and the non-stimulant atomoxetine, carry manufacturers' warnings contraindicating use in a range of cardiovascular disorders. These warnings include severe hypertension, heart failure, arterial occlusive disease, angina, congenital heart disease, cardiomyopathy, myocardial infarction, life-threatening arrhythmias, and channelopathies. Cerebrovascular disorders, including cerebral aneurysms, vasculitis, and stroke, also contraindicate use. Lisdexamphetamine, the prodrug of dexamphetamine, is contraindicated in symptomatic cardiovascular disease and moderate hypertension.

These contraindications arose from two observations: post-marketing surveillance reports of sudden death, stroke and myocardial infarction in adults taking CNS stimulant treatments; and sudden deaths in paediatric patients with structural cardiac abnormalities taking stimulants for ADHD[232,233]. In response to these naturalistic observations, two large retrospective cohort studies were conducted. The first included more than a million children and young adults, examined ADHD medicines (including methylphenidate, dexamphetamine, and atomoxetine), and failed to find any evidence of an increased risk of serious cardiovascular events[234]. The second examined over half a million participants between the ages of 25 and 64, and also failed to find any association between ADHD medication and an increased risk of cardiovascular events[235].

Since then, other studies have produced conflicting results. For example, a case-only study conducted in over a thousand children in South Korea found an increased risk

of arrhythmia and myocardial infarction[236]. Differences in study design may account for the varying results reported in the literature, reflecting the difficulty in studying an outcome that is extremely rare, particularly in children. Adults with ADHD are likely to have more risk factors for cardiovascular or cerebrovascular adverse events than children, being more likely to smoke, be obese, and take other medicines, as well as already having cardiac disease. ADHD itself may be an independent risk factor for developing cardiovascular disease[237]. Cohort studies in adults taking ADHD medication produce inconsistent results, some finding no increased risk of cardiovascular events (myocardial infarction or stroke) for any ADHD medication[235]. In contrast, a large cohort study in adults found an increased risk of ventricular arrhythmia in people taking methylphenidate, but the dose was inversely associated with risk, suggesting the association may not be causal[238]. Another cohort study found an increased risk of transient ischaemic attack in adult users of atomoxetine, but no increased risk of stroke[239].

Recent meta-analysis suggests overall no increased risk of cardiovascular disease with ADHD medication in adults or children (methylphenidate, amphetamines, and atomoxetine)[240], including in those with pre-existing cardiovascular disease, although the authors noted that more data are required and an increased risk of myocardial infarction or tachyarrhythmia could not be excluded. Lisdexamphetamine is comparatively less studied, but as a pro-drug of dexamphetamine has a similar safety profile to the other stimulants[241]. A cohort study in adult patients concluded that there was little or no increased risk of cardiovascular or cerebrovascular events in patients taking lisdexamphetamine, compared with those previously treated with other ADHD medication[242].

Older adults have an increased baseline risk for cardiovascular events, as well as being more likely to take several other drugs, increasing the likelihood of drug interactions and additive adverse effects. Fewer data are available for this population, and as for other age groups, published studies draw conflicting conclusions. One cohort study of stimulants in adults over 66 years found an increased risk of cardiac events (in particular, ventricular arrhythmia, stroke, or transient ischaemic attack) in the first 30 days of treatment[243], but the risk attenuated over time, with no association with cardiac adverse events at 6 or 12 months. Other studies that included older adults did not find any relationship with cardiac events[244], and a meta-analysis overall found no statistically significant association[240].

There is biological plausibility for an association with ADHD medicines and cardiovascular adverse events. The stimulants and atomoxetine are known to cause small rises in blood pressure and heart rate (they are sympathomimetic agents)[245,246]. Average blood pressure increases reported in studies are small (3 to 6mmHg systolic, 2 to 4mmHg diastolic), and some degree of tolerance may develop over time[247]. Average reported heart rate increases are 4 to 5bpm[247]. The stimulants and atomoxetine[247] are also proarrhythmogenic because of beta-adrenergic stimulation of the heart[248], potentially worsening atrial fibrillation or tachycardias, but it is not clear whether this translates into a direct association with adverse cardiac outcomes, as the previously described observational studies demonstrate. These drugs have also been shown to reduce heart rate variability and increase arterial stiffness[249]. Other sympathomimetic drugs have also been associated with adverse cardiac outcomes[250].

## Summary

The absolute contraindication of these medicines in cardiovascular disease is not cogently supported by current evidence[247]. Serious cardiac or cerebrovascular events in patients taking ADHD medicines are rare, and their risk may be outweighed by the benefits of the medication. Patients with pre-existing cardiovascular disease have a higher baseline risk of a further adverse event before adding to this risk with ADHD medication, and this should be considered when weighing against the potential benefits.

## Recommendations

- Be aware of the medicolegal implications of prescribing in context of a manufacturer's contraindication.
- Where possible, avoid the use of stimulants or atomoxetine in patients with cardiovascular or cerebrovascular disease. Use non-drug options or other medication in preference.
- Blood pressure and heart rate increases are not usually clinically significant. Some tolerance to the effects of the medicines on these parameters may develop over time. Do not stop the medication unless it is clinically necessary to do so.
- Patients with proarrhythmic cardiovascular diseases may be at particular risk from stimulants and atomoxetine. These drugs should only be used in this group of patients if there is clear benefit, and after other treatment options have been exhausted.
- The stimulant drugs and atomoxetine do not usually cause any apparent ECG changes. Therefore, ECG monitoring is probably of limited value in predicting a patient's risk of developing a drug-induced arrhythmia, or experiencing sudden cardiac death[247]. Nonetheless, a baseline ECG is recommended. The need for ongoing ECG monitoring should be discussed with a cardiologist.

# DRUG–DRUG INTERACTIONS[205,251,252]

There is a theoretical risk of additive hypotension when any antipsychotic or tricyclic antidepressant is given alongside an antihypertensive medicine.

## ACE inhibitors

ACE inhibitors can cause SIADH and resultant hyponatraemia. All antidepressants and antipsychotics, and carbamazepine, have been associated with the development of hyponatraemia – the risk is highest in the first weeks of treatment[21]. Monitor sodium levels in the first month of treatment, especially in patients with other risk factors for developing hyponatraemia.

The interaction between lithium and ACE inhibitors is well known. ACE inhibitors can cause dehydration (due to reduction in thirst), which can increase lithium plasma concentrations. They also increase renal sodium loss, which in turn also increases

lithium plasma concentrations. The magnitude of the effect is unpredictable. Some patients are unaffected, others experience four-fold increases in lithium levels[12]. If the combination is unavoidable, monitor lithium plasma concentrations and renal function closely (weekly until stable, then at least 3 monthly).

## Angiotensin-II antagonists

There are case reports of lithium toxicity when given with the angiotensin-II antagonists candesartan, losartan, valsartan, and irbesartan. Similar to the ACE inhibitors, the angiotensin-II inhibitors inhibit aldosterone secretion in the kidneys, resulting in increased sodium loss by the renal tubules. This causes lithium retention and a risk of toxicity. The effect is not as marked as it is for ACE inhibitors, and evidence in clinical use is limited to a few case reports. As for ACE inhibitors, monitor lithium plasma concentrations weekly until stable (which may take up to eight weeks).

## Beta blockers

Sotalol has a high risk of prolonging the QT interval. Combination with antidepressants, especially TCAs, citalopram, and escitalopram, should be avoided. Similarly, avoid the combination of sotalol with antipsychotics that prolong the QT interval, or lithium. Duloxetine, fluoxetine, and paroxetine (and to a lesser extent, citalopram and escitalopram) inhibit CYP2D6, and so may increase exposure to propranolol, metoprolol, carvedilol, and nebivolol.

## Calcium channel blockers

The non-dihydropyridine calcium channel blockers diltiazem and verapamil are moderate inhibitors of CYP3A4. There is therefore a theoretical risk of an increased plasma concentration of drugs such as trazodone, vilazodone, cariprazine, lurasidone, lumateperone, brexpiprazole, iloperidone, risperidone, paliperidone, quetiapine, droperidol, sertindole, and pimozide.

Concurrent use of cariprazine and CYP3A4 inhibitors is contraindicated by the UK manufacturers. The FDA allows prescribing with strong CYP3A4 inhibitors, with dose adjustment of cariprazine. It recommends reducing the dose by half, or to alternate days for patients taking 1.5mg. New starters of cariprazine should be started at 1.5mg on day 1 and 3 (no dose on day 2), then 1.5mg daily, up to a maximum of 3mg. Lumateperone doses should be reduced to 21mg daily if given with diltiazem or verapamil, and lurasidone doses should be halved. Brexpiprazole doses should be reduced if a concurrent CYP2D6 inhibitor is also given. The UK manufacturers of sertindole contraindicate diltazem and verapamil, principally because if a patient is also a poor metaboliser of CYP2D6, the CYP3A4 pathway becomes more important. This seems overcautious. In the UK, quetiapine is contraindicated with all CYP3A4 inhibitors, based on evidence of increased plasma concentrations with strong inhibitors such as ketoconazole. Advice is more nuanced in the USA, where dose reductions to one sixth of the original dose are recommended only with strong inhibitors.

TCAs are predominantly metabolised via CYP2D6, but 3A4 is a minor pathway. This may explain observations in a few case reports and one crossover study of increased plasma concentrations of trimipramine, nortriptyline and imipramine when combined with verapamil, and in particular diltiazem. The crossover study[253] (conducted in 12 healthy males, ethnicity not reported) showed an increase in plasma concentrations of a single dose of imipramine of 15% when given with verapamil, and 30% when given with diltiazem. Two of the participants developed second-degree heart block on the combination of imipramine and verapamil. A mean PR interval of >200ms was observed in both diltiazem and verapamil groups, representing first-degree heart block. Beyond this study, there is scant evidence for a clinically significant interaction between calcium channel blockers and TCAs. The combination is not contraindicated, or even cautioned by manufacturers. TCAs should be avoided in patients with significant cardiac disease, but if they are to be used in combination with diltiazem or verapamil in a patient at particular risk of heart block, monitor the ECG and dose cautiously.

Carbamazepine reduces the concentration of calcium channel blockers (it is a potent CYP3A4 inducer). Conversely, carbamazepine is also metabolised by CYP3A4, and so the moderate inhibitors diltiazem and verapamil may increase carbamazepine concentrations. Use plasma concentrations to guide dosing. There are some reports of neurotoxicity and alterations in lithium plasma concentrations when lithium is given with calcium channel blockers, but also reports of uneventful use. The mechanism for a potential interaction is unclear.

## Sacubitril/valsartan

No interactions, but note that the manufacturer mentions hallucinations, paranoia, and sleep disturbance (in the context of psychotic events). The cautions described for angiotensin-II inhibitors also apply here.

## Spironolactone/eplerenone

The manufacturer of eplerenone cautions against the combination with lithium, apparently because of the risk of lithium toxicity with diuretics and ACE inhibitors. There is no clear evidence of a serious interaction between lithium and potassium-sparing diuretics, but measuring lithium plasma levels on initiation would be wise. There is also a manufacturer's warning of the risk of hypotension with all 'neuroleptics' (antipsychotics), and tricyclic antidepressants when combined with eplerenone. Exposure to eplerenone may be reduced by the CYP3A4 inducer carbamazepine.

## Ivabradine

Ivabradine causes bradycardia, which increases the risk of torsade de pointes in people with a prolonged QTc – caution should be exercised when combining with antidepressants or antipsychotics that prolong the QT, or lithium. Due to CYP3A4 induction, carbamazepine may reduce the plasma concentration of ivabradine.

## 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[254], but this is disputed. Clinically significant problems are highly unlikely.

## Hydralazine

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

## Nitrates

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

## Loop diuretics

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

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 QT interval (TCAs, citalopram, escitalopram, antipsychotics, lithium).

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, antipsychotics, and carbamazepine. Monitoring of sodium is advised, especially in the first 4 weeks of treatment and in patients with additional risk factors for hyponatraemia.

The manufacturers of risperidone advise particular caution when combining it with furosemide in elderly patients with dementia. This is because of a finding in two placebo-controlled studies of an increase in mortality with the combination. The reason for this is not clear (thiazide diuretics do not appear to have this association), but dehydration is a known risk factor for mortality. The use of the two drugs together is not contraindicated, but in practice if alternatives can be used, this would seem sensible.

Loop diuretics can cause increases in lithium plasma concentrations, possibly because of increased sodium loss and resorption. Many patients experience no difficulties with the combination, but there are reports of serious lithium toxicity. Monitor lithium plasma concentrations more frequently (ideally weekly) for the first month when starting the combination.

## SUMMARY OF RECOMMENDATIONS

| | Antidepressant | Antipsychotic | Mood stabiliser |
|---|---|---|---|
| Heart failure | Sertraline. Avoid TCAs. | Cariprazine, brexpiprazole, lumateperone or lurasidone. Avoid olanzapine. Note that clozapine may not be contraindicated. | No obvious optimal choice; see text. |
| Coronary heart disease | Sertraline, or mirtazapine if significant bleeding risk. | Cariprazine, brexpiprazole, lumateperone or lurasidone. | Lithium, lamotrigine. If using valproate or pregabalin monitor weight. Avoid carbamazepine. |
| Hypertension | Sertraline | Any, but avoid olanzapine and possibly risperidone. | Any |
| Anticoagulation | Mirtazapine, agomelatine | Any | Lithium, lamotrigine, pregabalin. Avoid carbamazepine and possibly valproate. |
| Stroke | Mirtazapine | No obvious optimal choice, see text. Avoid weight gain. | Lithium, valproate, lamotrigine, pregabalin. Avoid carbamazepine. |
| Atrial fibrillation | Mirtazapine or agomelatine. SSRIs can be used, but beware of the interaction with warfarin and other anticoagulants. | Cariprazine, brexpiprazole, lumateperone, or lurasidone. | Any |

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