Heart and mind: (2) psychotropic and cardiovascular therapeutics
S U Shah, Z Iqbal, A White, S White

There is a plausible biological basis for the association between psychiatric morbidity and cardiovascular disease. Anxiety, panic disorder, and depression are common in patients with coronary heart disease and hypertension. Despite this evidence there is poor recognition of anxiety disorders and depression in primary care and hospital medical practice. Concern also surrounds the use of psychotropic drugs in patients with cardiovascular disease. In the first of the two articles on this subject, we highlighted the current evidence regarding the association between cardiovascular and psychotropic conditions. In this second article, we discuss the interaction of the drugs used in the management of these two varied but commonly coexistent group of diseases as well as their relative effects on either system. Finally, we summarise the data regarding the safe use of these medications based on the recommendations from the currently available evidence.

In the companion paper to this article, we highlighted the association between neuropsychiatric illnesses and cardiovascular diseases.1 Both conditions, in particular depression and ischaemic heart disease, are common in the general population. Indeed, the Global Burden of Disease Study found that depression is second only to ischaemic heart disease as a cause of disability and early death in industrialised countries.2 Although rates of depression are high in the general community, they are even higher in patients with cardiac illnesses. Other psychiatric conditions such as anxiety disorders and psychotic illnesses such as schizophrenia are also not uncommon. Given the wide prevalence of both sets of disease, it is quite likely that in a considerable number of patients these illnesses will coexist. Drugs used to treat depressive and psychotic conditions in particular have been shown to have significant cardiac effects and important pharmacological interactions with medications used to treat cardiovascular diseases. Conversely, some cardiac drugs have also been implied in causing psychiatric symptoms. It is therefore important to understand the actions, side effects, and interactions of the drugs used in treatment of these two varied groups of diseases.

A comprehensive discussion of these effects and interactions is beyond the scope of this review, which is mainly addressed to cardiologists and other medical physicians. Readers should refer to other texts for a more in-depth review. In the following sections we will briefly discuss the pharmocological profiles, cardiac actions, and side effects of the major classes of psychotropic drugs. In addition, we will also review the neuropsychiatric effects of commonly used cardiovascular drugs. In the final sections, we will highlight and summarise the recommendations for use of psychotropic medications in specific cardiovascular disorders.

EPIDEMIOLOGY
Although there are no exclusive data on the extent of cardiac effects and interaction of psychotropic medication with drugs used in treating cardiovascular conditions, some inference can be derived from the epidemiological, observational, and anecdotal evidence available from various sources. Medications range from the anxiolytics that, in general, are relatively safe with minimal cardiac effects, to antidepressants (tricyclic and monoamine oxidase inhibitors antidepressants in particular) and antipsychotics that have been shown to have multiple cardiac effects including increased incidence of cardiac arrhythmias and possibly sudden cardiac death.

Because many cardiac and psychotropic agents lower blood pressure, additive hypotensive effects are not uncommon, as for example between the tricyclic antidepressants and anti-hypertensives. Many psychotropic agents slow conduction and prolong the PR, QRS, and QT intervals, and synergistic effects can occur when they are used in conjunction with antiarrhythmic medications, resulting in heart block or the long QT syndrome. Selective serotonin reuptake inhibitors (SSRIs; for example, fluoxetine, sertraline, paroxetine, and fluvoxamine) are bound to plasma proteins and can displace other protein-bound drugs, thereby increasing the level of active drug and resulting in possible toxicity.

Antipsychotic (neuroleptic) drugs have generally been regarded as a group of drugs with a good margin of safety, but there have been regular case reports of sudden death associated with these agents since the 1960s.3–6 The part played by antipsychotic drugs is often uncertain, but when sudden death occurs in previously healthy young individuals a common conjecture is that medication was responsible. This concern follows several reports of unexpected deaths in young people, usually males, where the concurrent prescription of antipsychotic drugs has

See end of article for authors’ affiliations

Correspondence to:
Dr Saeed Ullah Shah,
Department of Cardiology,
Ysbyty Gwynedd, Bangor,
North Wales, UK;
saeedshah@miranshah.
freeserve.co.uk

Submitted
19 September 2003
Accepted 7 August 2004

Abbreviations: CSM, Committee on Safety of Medicines;
GABA, gamma amino butyric acid; SSRI, selective serotonin reuptake inhibitor

www.postgradmedj.com
been implicated.7 8 There are insufficient data to prove that sudden death is more likely among people being treated with antipsychotic medication than it is among the general population. However, there are no data that prove that there is no causal relationship between the use of this group of drugs and sudden death. Further, the Committee on Safety of Medicines (CSM) has received reports of 31 cases of unexplained sudden death and 63 reports of fatal cardiac arrest/arrhythmias in association with people treated with various antipsychotic drugs, covering the period that each drug was introduced up to May 1996.9

Abnormalities seen on electrocardiography are relatively common in people receiving neuroleptics, occurring in around 25% of patients receiving this class of medications.10 11 There are numerous reports of ventricular arrhythmias associated with repolarisation disturbances such as prolonged QT intervals, widening of QRS complexes, depression of ST segments, and most commonly abnormal T morphology or large U waves.12–19 They are observed more often in patients with pre-existing heart disease.20 In another study, QTc (QT interval corrected for heart rate) prolongation (>420 ms) was found to be significantly more common (23%) in a sample of 111 chronic inpatients with schizophrenia receiving antipsychotic medication than in 42 age matched, drug-free controls.11 12

Thioridazine and, less frequently, chlorpromazine have been particularly implicated in the development of ventricular tachycardia, primarily in patients taking overdoses.21 Thioridazine in particular was found to be significantly more likely to cause tachycardia, a prolonged QT interval, prolonged QTc (>450 ms), a widened QRS (>100 ms), and arrhythmias.22–24 Electrocardiographic abnormalities have also been found in 10% of patients treated with pimozide.25

Indeed, from 1971 to 1995, the CSM received 40 reports (16 fatal) of serious cardiac reactions, predominantly arrhythmias, with pimozide.26 It has also been suggested that antipsychotic drugs may be responsible for a toxic cardiomyopathy, leading to death by ventricular fibrillation or cardiac arrest. Ultrastructural damage to the heart associated with circulating autoantibodies, especially those to skeletal muscle, heart, DNA, mitochondria and smooth muscle, has been found in patients who have died from drug related, fatal arrhythmias.27 Further, clozapine has been associated with myocarditis, which has been found in cases of sudden death.28–30

Data regarding tricyclic antidepressants and the mortality associated with this cardiac effect are also not straightforward. Cardiac effects are generally associated with ingestion of bigger doses and in vulnerable patients. Although not all deaths or hospital admissions associated with the use of antidepressants are due to their cardiac effects, however, it will contribute to the majority of these incidents. Overall, the average death rate associated with single-ingested antidepressant toxicity is 0.00034 per year of treatment. In other words, one fatality may be expected for about every 3000 patients treated for one year. However, tricyclic antidepressants (excluding lofepramine) have a substantial cardiovascular toxicity and a higher associated fatality rate, 0.00058 per year of treatment, approximately one fatality for every 1750 patients treated for one year. SSRIs as a group are relatively safe, with a group fatality rate of 0.00001 per year of treatment, approximately one fatality for every 100 000 patients treated for one year. One second generation tricyclic antidepressant appears atypical: lofepramine features a fatality rate similar to the SSRIs of 0.000017 per year of treatment, approximately one fatality for every 59 000 patients treated for one year, and statistically this is not significantly different from the SSRIs as a group.31 It is only possible to make reasonable estimates of toxicity where substantial use is made of specific drugs. One or more of the lesser used tricyclic or related antidepressants may have relatively safe toxicity, but this is uncertain.

USE OF PSYCHOTROPIC DRUGS IN CARDIOVASCULAR CONDITIONS (TABLE 1)

Anxiolytics/hypnotics

Of the anxiolytics and hypnotic agents used to treat anxiety and sleep disorders, benzodiazepines and the newer hypnotics are now the most widely used group. Approximately 20 benzodiazepines derivatives are currently available. They bind to specific, high affinity sites on the cell membrane parallel to the receptors for gamma amino butyric acid (GABA). The binding of benzodiazepines increases the affinity of GABA receptors for this neurotransmitter causing hyperpolarisation and inhibition of neural firing. Benzodiazepines are used in treating the anxiety that accompanies some form of depression and schizophrenia. They are very useful in treating panic disorders and are also used as sedatives, anticonvulsants, and muscle relaxants.

Anxiety disorders, especially panic and generalised anxiety disorder and disturbed sleep pattern, are prevalent in patients with cardiac disease. Hospitalised cardiac patients are acutely anxious, and because anxiety itself can threaten cardiac status, benzodiazepines have been widely used in coronary care units. They are considered as one of the safest groups of drugs in cardiovascular diseases. They are generally shown to be free of cardiac side effects and can be used safely in seriously ill cardiac patients, even in the period immediately after myocardial infarction.32 They can, however, decrease respiratory drive in patients with chronic obstructive pulmonary disease and chronic hypercapnia. No significant work has been done to assess the effects of using benzodiazepines on cardiac mortality or morbidity. In one small study, however, diazepam was shown to reduce myocardial contractility and increase myocardial blood flow by probably causing coronary vasodilatation when given intravenously.33 Overall, given the paucity of work done in this field, it would be prudent to restrict the use of anxiolytics for a short period of time if indicated in an acute cardiac event.

Larger doses of hypnotic agents can cause respiratory insufficiency and could thus indirectly affect vulnerable cardiovascular patients. Barbiturates are more toxic and should be completely avoided in cardiac conditions. Chloral hydrate is contraindicated in severe heart disease, particularly in heart failure, where it has been shown to react with frusemide.34

Antidepressants (tables 2 and 4)

Major depression is an insidious mood altering condition affecting sleep, appetite, libido, and the ability to function. Cross sectional and case-control studies have shown that rates of depression are higher among patients with coronary artery disease. Follow up of patients after myocardial infarction has shown that they have a worse prognosis than non-depressed patients. Antidepressants are generally used effectively in treating a whole range of depressive disorders. The main classes of antidepressants include tricyclic/polycyclic agents, SSRIs, serotonin and noradrenaline (norepinephrine) reuptake inhibitors, and monoamine oxidase inhibitors.

Tricyclic antidepressants inhibit the neuronal reuptake of noradrenaline and serotonin into presynaptic nerve terminals. By blocking the major route of neurotransmitter removal, they lead to increased concentrations of monoamines in the synaptic cleft, resulting in antidepressant effects. They also block serotonergic, α-adrenergic, histaminergic, and muscarinic receptors. The important drugs in this group are imipramine, amitriptyline, desipramine, nortriptyline, protriptyline, and doxepin. SSRIs are chemically unique antidepressants. They specifically inhibit serotonin reuptake.
They, therefore, have fewer anticholinergic and thus cardiac side effects. Serotonin and noradrenaline reuptake inhibitors are the newest antidepressant agents. They block the neuronal reuptake of serotonin and noradrenaline. Monoamine oxidase inhibitors are the least used antidepressants. They irreversibly or reversibly inactivate this enzyme, leading to accumulation and increased concentrations of this neurotransmitter in the synaptic space. This causes activation of noradrenergic and serotonin receptors and may be responsible for the antidepressant action of these drugs.

Tricyclic antidepressants have multiple cardiovascular side effects. They increase catecholamine activity resulting in cardiovascular stimulation. The tricyclic antidepressants have type 1a antiarrhythmic properties (quinidine-like

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Safety of psychotropic drugs in cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Lower risk</strong></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Amisulpride</td>
</tr>
<tr>
<td></td>
<td>Butyrophenones</td>
</tr>
<tr>
<td></td>
<td>Flupentixol</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
</tr>
<tr>
<td></td>
<td>Sulpiride</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Mianserin</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
</tr>
<tr>
<td></td>
<td>Tryptophan</td>
</tr>
<tr>
<td></td>
<td>Viloazine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Vigabatin</td>
</tr>
<tr>
<td>Antialalytics + hypnotics</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Buspirone</td>
</tr>
<tr>
<td></td>
<td>Zopiclone</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Acamprosate</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Commonly used antidepressants, dosages, general and cardiovascular side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Starting dose</strong></td>
</tr>
<tr>
<td>Sertraline</td>
<td>12.5–25 mg/day</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5–10 mg/day</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Tricyclics</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10–25 mg at bedtime</td>
</tr>
<tr>
<td>Imipramine</td>
<td>10–25 mg at bedtime</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Desipramine</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Other agents</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>12.5 mg twice a day</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 mg every hour of sleep</td>
</tr>
</tbody>
</table>
This side effect is more likely to be clinically
particularly in the elderly, may have serious consequences such
in up to 20% of patients. This cardiovascular effect, particu-
larly caused by their prolongation of the QT interval and/
or an increase in myocardial noradrenaline resulting from
the peripheral inhibition of noradrenaline reuptake.
Although the most common arrhythmias are atrial or ven-
tricular premature beats, these may give way to more maling-
nant ventricular arrhythmias. These toxic, proarrhythmic
effects are seen primarily in overdose, and at therapeutic
levels they are rare and more likely in those with pre-existing
ischaemic heart disease, a prolonged QT interval, electrical
instability, or a recent myocardial infarction. At toxic levels,
any type of arrhythmia may be seen. These may last for three
to four days after ingestion. Tricyclic antidepressants also
raise heart rate by 5–20 beats per minute, as a result of their
antiadrenergic blockade. They also block α-adrenergic recep-
tors causing orthostatic hypotension and a reflex tachycardia
in up to 20% of patients. This cardiovascular effect, particu-
larly in the elderly, may have serious consequences such
as acute coronary syndromes, cerebral hyperperfusion, and
falls. This side effect is more likely to be clinically
significant in patients with chronic heart failure, impaired
left ventricular function, volume depletion, or in patients
who are taking antihypertensive medications. There are also
several interactions between the tricyclics and cardiac medica-
tions. The tricyclics interfere with neuronal reuptake of clonidine and guanethidine and thus antagonise their
antiadrenergic action. They may potentiate the antihyper-
tensive action of prazosin, and the dry mouth induced may
hinder the absorption of sublingual nitrates. Taking all this
action). As shown in the Cardiac Arrhythmia Suppression
Trial, use of drugs with class Ia or Ic are associated with
increased mortality in patients with ischaemic heart disease
and therefore should be avoided in such patients. Owing
to their antiarrhythmic properties, they can slow cardiac
conduction, decrease ventricular irritability, and suppress
eccentric activity. In the absence of pre-existing conduction
abnormalities, this action is unlikely to be clinically signi-
ficant at therapeutic doses. However, second degree heart
block, sick sinus syndrome, bundle branch block, a prolonged
QT interval, and the concurrent administration of anti-
arrhythmic agents are all considered contraindications to
their use.

In contrast to this antiarrhythmic effect, tricyclic anti-
depressants can on occasion be arrhythmogenic. This is
probably caused by their prolongation of the QT interval and/
or an increase in myocardial noradrenaline resulting from
peripheral inhibition of noradrenaline reuptake. Although
the most common arrhythmias are atrial or ven-
tricular premature beats, these may give way to more maling-
nant ventricular arrhythmias. These toxic, proarrhythmic
effects are seen primarily in overdose, and at therapeutic
treatment levels they are rare and more likely in those with pre-existing
ischaemic heart disease, a prolonged QT interval, electrical
instability, or a recent myocardial infarction. At toxic levels,
any type of arrhythmia may be seen. These may last for three
to four days after ingestion. Tricyclic antidepressants also
raise heart rate by 5–20 beats per minute, as a result of their
antiadrenergic blockade. They also block α-adrenergic recep-
tors causing orthostatic hypotension and a reflex tachycardia
in up to 20% of patients. This cardiovascular effect, particu-
larly in the elderly, may have serious consequences such
as acute coronary syndromes, cerebral hyperperfusion, and
falls. This side effect is more likely to be clinically
significant in patients with chronic heart failure, impaired
left ventricular function, volume depletion, or in patients
who are taking antihypertensive medications. There are also
several interactions between the tricyclics and cardiac medica-
tions. The tricyclics interfere with neuronal reuptake of clonidine and guanethidine and thus antagonise their
antiadrenergic action. They may potentiate the antihyper-
tensive action of prazosin, and the dry mouth induced may
hinder the absorption of sublingual nitrates. Taking all this
into account, tricyclic antidepressants should be avoided in
ischaemic heart disease in particular and other cardiovascular
conditions in general.

Bupropion, a non-tricyclic antidepressant that acts on both
the dopamine and noradrenaline systems, causes less hypo-
tension than the tricyclic antidepressants; does not affect
cardiac rate, conduction, or contractility; and is safely used
in patients with cardiac disease. It does not exacerbate ventri-
cular arrhythmias or conduction block in patients with these
conditions.

SSRI antidepressants are considered relatively safer. The
SSRIs have superseded tricyclic antidepressants as the first
line agents for treating the cardiac patient with major
depressive disorder. In healthy patients, the SSRIs have no
adverse effects on cardiac contractility or conduction and
there is no evidence of cardiotoxicity in overdose. In patients
with cardiac disease, they do not appear to cause significant
electrocardiographic or blood pressure changes, although
they can slow heart rate. More extensive investigation is still
necessary, but the data thus far suggest that the SSRIs have
minimal cardiovascular effects and a large margin of safety in
treating patients with even very severe heart disease. The
SSRIs have, however, the potential to interact with a number of
medications used to treat cardiac disease as they inhibit
hepatic cytochrome P450 isoenzymes. This is particularly
salient with warfarin and digoxin, although the clinical
significance of these interactions is not yet clear.

Venlafaxine, the new serotonin and noradrenaline reup-
take inhibitor antidepressant, affects the reuptake of both
serotonin and noradrenaline. It appears to have very few
cardiovascular actions and no effect on the electrocardio-
gram. At higher doses, however, venlafaxine has been associ-
ated with an increase of blood pressure. Unlike the SSRIs,
it does not inhibit P450 cytochrome isoenzymes and may
therefore be useful in patients on cardiac medications.

### Table 3  Neuropsychiatric side effects of common cardiovascular medications

<table>
<thead>
<tr>
<th></th>
<th>Agitation/anxiety</th>
<th>Delirium</th>
<th>Depression</th>
<th>Hallucinations</th>
<th>Mania hypomania</th>
<th>euphoria</th>
<th>Seizures</th>
<th>Sleep problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diltiazem (2.4%)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Felodipine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mexiletine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nicardipine (rare)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prazosin</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Procainamide</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quinapril</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reserpine</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spiranolactone</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Streptokinase</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Antipsychotics

Antipsychotic drugs are used in the treatment of schizo-
phrenia, organic psychoses, and mood disorders with psychot-
ic features. They are also widely used in geriatric patients for
agitation, confusion, excitement, and behavioural disinhibi-
tion. All antipsychotics block dopamine receptors in the brain
and in the periphery. The newer atypical agents appear to
Exert part of their unique action through inhibition of serotonin receptors. The antipsychotic action of neuroleptic drugs reflect blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic and histamine receptors, causing a variety of side effects.

Antipsychotic use has been shown to have significant cardiac side effects. In general, these drugs affect cardiac conduction and rhythm and produce hypotension. They have α-adrenergic blocking and quinidine-like properties, along with anticholinergic activity. They can produce prolongation of the PR and QT intervals, ST segment depression, T wave changes, ventricular arrhythmias, and heart block. Although the quinidine-like effects of the neuroleptics are usually negligible, they can become significant in patients already taking type I antiarrhythmics.46 When administering a low potency neuroleptic along with an antiarrhythmic, electrocardiography should be used to monitor for conduction delays. When these agents are used together with antihypertensive agents there is more chance of orthostatic hypotension. This is of particular concern in the elderly and in acute myocardial infarction.

The higher potency neuroleptic agents, such as haloperidol and the piperazine phenothiazines, produce fewer of these effects and are therefore preferred in the presence of significant cardiac disease (especially conduction problems) and after cardiac surgery.46 Haloperidol in particular has been frequently used with safety and efficacy in severely ill cardiac patients. Oral haloperidol does not significantly affect the electrocardiogram, and intravenous haloperidol is used in acute emergencies such as agitated deliria. Intravenous administration may cause torsades de pointes, and the QT interval should therefore be monitored during aggressive, intravenous haloperidol therapy.47

Experience with the newer, “atypical” antipsychotics in cardiac patients is much more limited but suggests a generally similar profile. Clozapine can cause tachycardia and orthostatic hypotension and has significant anticholinergic activity. There are recent reports of an infrequent association of clozapine with electrocardiographic changes, arrhythmias, myocarditis, and congestive heart failure.48 49 Olanzapine produces mild orthostatic hypotension but has little effect on the electrocardiogram. Sertindole prolongs the QT interval and may therefore pose a problem in cardiac patients. Risperidone produces hypotension and has a quinidine-like effect, prolonging the QT interval, although this may occur only in overdose.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Interactions of psychotropic and cardiac medications: interactions involving tricyclic antidepressants and serotonergic antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Effect on cardiac agent</td>
</tr>
<tr>
<td>Interactions involving tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Type I antiarrhythmics</td>
<td>Potentiate delay in cardiac conduction; heart block</td>
</tr>
<tr>
<td>Antihypertensives: guanethidine, clonidine, reserpine</td>
<td>Antagonise antihypertensive effect; potentiate orthostatic hypotension</td>
</tr>
<tr>
<td>Sublingual nitrates</td>
<td>Oral absorption hindered by dry mouth</td>
</tr>
<tr>
<td>α-Adrenergic blocking agents</td>
<td>Potentiate antihypertensive effect</td>
</tr>
<tr>
<td>Interactions involving serotonergic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Lipophilic β-blockers</td>
<td>Increase blood levels due to decreased hepatic degradation</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Type Ic antiarrhythmics</td>
<td></td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Increase bioavailability due to displacement from protein-binding sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Interactions of psychotropic and cardiac medications: interactions involving lithium and carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Effect on psychotropic or cardiac agent</td>
</tr>
<tr>
<td>Interactions involving lithium</td>
<td></td>
</tr>
<tr>
<td>Diuretics that cause sodium loss</td>
<td>Increase blood lithium levels</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Enhance lithium toxicity; bradycardia</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Enhance lithium toxicity</td>
</tr>
<tr>
<td>Methylidopa</td>
<td>Enhance lithium toxicity</td>
</tr>
<tr>
<td>Interactions involving carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Antiaarrhythmics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Interactions involving lithium</td>
<td></td>
</tr>
<tr>
<td>Diuretics that cause sodium loss</td>
<td>Increase blood lithium levels</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Enhance lithium toxicity; bradycardia</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Enhance lithium toxicity</td>
</tr>
<tr>
<td>Methylidopa</td>
<td>Enhance lithium toxicity</td>
</tr>
<tr>
<td>Interactions involving carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Antiaarrhythmics</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Psychotropic drugs known to prolong the QT interval of the electrocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Sulfapiride</td>
<td>Maprotiline</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Others</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Others</td>
</tr>
<tr>
<td>Perphenazine</td>
<td></td>
</tr>
</tbody>
</table>
Use great caution with lithium and changes in diuretic dosage. 

In its acute stages avoid using those medications which cause hypotension—for example, phenothiazines, clozapine, risperidone, and tricyclic antidepressants should be avoided.

Lithium salts (table 5)

Lithium is used prophylactically in treating manic-depressive patients and in the treatment of manic episodes. They are also effective in treating 60%–80% of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with lithium salts, the exact mode of action is unknown. It is currently proposed that lithium acts by altering the cellular concentration of a second messenger, inositol triphosphate.

In therapeutic doses, lithium exerts minimal cardiotoxicity in the majority of patients. It can be used safely in cardiac disease if initiated at a low dose, increased gradually, and monitored carefully. Benign, reversible T wave changes (including inversion and flattening) are common with lithium administration and are not clinically significant. Clinically significant cardiovascular side effects of lithium are more rare. 

If any of the above are abnormal, or a QT interval and T wave changes are present, seek a specialist cardiology opinion.

Box 1: Summary (how to manage patients with heart disease)

- Monitor drugs causing orthostatic hypotension, particularly in the elderly.
- Avoid monoamine oxidase inhibitors, as they interact with many medications and therefore can affect the actions of other antihypertensives in a beneficial or dangerous manner.
- Venlafaxine in higher doses, clozapine, rarely tricyclic antidepressants and antipsychotics. can increase blood pressure.
- SSRIs and benzodiazepines are relatively safe to use.

Stable ischaemic heart disease

- Avoid using drugs causing orthostatic hypotension, which may exacerbate angina.
- Avoid using drugs causing tachycardia—for example, phenothiazines, clozapine, risperidone.
- Use SSRIs, as they are considered safer than tricyclic antidepressants, which may cause tachycardia or a quinidine-like effect. Avoid trazadone and nefazadone.

Acute myocardial ischaemia/period after myocardial infarction

- Avoid all antidepressants if possible for two months after myocardial infarction.
- If required, use only SSRIs (except fluvoxamine and citalopram which may be more cardiotoxic in larger doses/over doses).
- Avoid tricyclics. Because of their class Ia proarrhythmic properties, they may increase subsequent mortality.
- Avoid high dose antipsychotics. They can cause orthostatic hypotension and tachycardia, besides having a direct cardiac muscle suppressant effect in patients after myocardial infarction. Avoid pimozide in patients with any cardiac abnormality.
- Clozapine should be started slowly and with caution less than a year after myocardial infarction or in cardiac disease; olanzapine may be a safer alternative in the acute period after myocardial infarction.
- Anxiolytics are often prescribed because anxiety is not only uncomfortable but its concomitant sympathetic arousal can be medically dangerous. Benzodiazepines are most commonly used for this purpose and should be prescribed on a regular, round-the-clock (rather than as needed) basis.
- In the elderly and in those with compromised liver function, the shorter acting benzodiazepines (for example, oxazepam or lorazepam) are preferred, because they are cleared primarily by the kidneys.

Heart failure

- In its acute stages avoid using those medications which cause hypotension—for example, phenothiazines, clozapine, risperidone, and tricyclic antidepressants.
- β-Blockers used for psychiatric illnesses in acute cases of heart failure should be withdrawn or their dose lowered according to patient clinical status.
- Use great caution with lithium and changes in diuretic therapy.

Box 2: Management of a patient with a long QT interval and requiring antipsychotic medication

- Take a careful cardiac history, remember to ask for a family history of syncope or sudden cardiac death.
- Palpitations, presyncope or syncope, spontaneously or in response to stress, shock or exertion, should prompt a cardiac referral, even in the presence of normal electrocardiography.
- Perform a careful physical examination to exclude another cardiac or neurological disorder.
- Perform a 12 lead electrocardiogram. Bear in mind that the presence of a normal QTc does not exclude the possibility of a QT interval anomaly.
- Take blood for serum potassium, calcium, magnesium, and thyroid hormone estimation. Abnormalities of these factors are potent causes of arrhythmia, and may exacerbate other causes of QT interval prolongation. The levels should be monitored and maintained within the normal range.
- If any of the above are abnormal, or a QT interval problem is still suspected, reduce or withhold medication if appropriate and seek a specialist cardiology opinion.
- If medication is essential, avoid prescribing thiourida zine, chlorpromazine, or high doses of depot medication. Consider the use of adjunctive medicines such as benzodiazepines to manage acute situational disturbances, rather than high doses of antipsychotics of any class.
possible toxicity when combined with lithium. Lithium toxicity precipitated by the use of angiotensin and of bradycardia when lithium is coadministered with the cardiovascute medications are considered. Cardiac effects, however, are relatively more common in the older anticonvulsive patients with background cardiac illnesses such as ischaemic heart disease, arrhythmias, and heart failure. Gabapentin and lamotrigine, the relatively newer antiepileptic agents, have a favourable pharmacokinetic profile compared with other antiepileptic drugs. In general, they have no significant cardiac effects, few other side effects, and are better tolerated than other antiepileptic drugs.56–58

### References

5. Reference withdrawn.

### Authors’ affiliations

S U Shah, University Hospital Birmingham and University of Birmingham, Birmingham, UK
Z Iqbal, Department of Cardiology, Ysbyty Gwynedd, Bangor, North Wales, UK
A White, S White, University Hospital Birmingham, Birmingham, UK

### Cardiac considerations of patients requiring psychotropic medications

- History of arrhythmias, heart failure, myocarditis, and acute coronary syndromes in the preceding three months.
- Congenital long QT interval.
- Concurrent digoxin therapy.
- Concurrent use of other medicines associated with QT interval prolongation.
- History of substance misuse or heavy alcohol consumption.
- Severe hepatic or renal impairment.
- Elderly and the malnourished patients.
- Hypokalaemia.
- Hypothyroidism.
- Routine electrocardiographic monitoring for patients receiving high doses of thyroid hormones.
- Availability of resuscitation when using intravenous medications.
- Mandatory training in cardiopulmonary resuscitation for hospital staff.
- Particular caution with dosage in patients who are likely to be particularly susceptible to cardiovascular effects, especially those receiving class I and II cardiac antiarrhythmic drugs, frequent ventricular ectopy.
- Avoidance of other medications that may increase the risk of cardiovascular reactions such as tricyclic antidepressants; SSRIs; erythromycin; and antihistamines.

very rare; they may include sinus node dysfunction and increases in ventricular irritability. In patients with heart failure, low cardiac output and low glomerular filtration, diuretic use can increase lithium levels as hypotension may decrease renal clearance of lithium. Lithium may still be administered to the patient on diuretics, but lithium levels must be monitored and lithium dosage may need to be reduced as much as 25% to 50%, although during acute diuresis the proper adjustment of lithium is difficult because of the massive shifts in sodium and fluid balance. The elderly also require lower lithium doses because of a decline in the glomerular filtration rate. On rare occasion, lithium may worsen arrhythmias in patients with sinus node dysfunction. There are also reports of idiosyncratic toxic reactions and of bradycardia when lithium is coadministered with the calcium channel blockers verapamil and diltiazem, and of lithium toxicity precipitated by the use of the antiepileptic agents. Converting enzyme inhibitors. Methyldopa seems to have a number of interactions with psychotropic agents, including possible toxicity when combined with lithium.

### Anticonvulsants

Antiepileptics as a group are considered reasonably safe drugs when their cardiac side effects and interaction with cardiovascular medications are considered. Cardiac effects, however, are relatively more common in the older anticonvulsive agents such as sodium valproate, carbamezepine, and phentoin. Overdose with valproate has been shown to cause cardiac conduction problems including heart block. It can also lower the platelet count and fibrinogen levels and therefore can increase the prothrombin time. Carbamazepine can also induce cardiac conduction abnormalities and heart blocks. It is known that it has quinidine-like effects and can aggravate heart block and exacerbate chronic heart failure. Carbamazepine can also produce hypotension, and this effect is potentiated by other factors that cause hypotension, such as diuretics and heart failure. The metabolic degradation of carbamazepine may be inhibited by calcium channel blockers, thereby increasing the risk of carbamazepine toxicity. Carbamazepine and antiarrhythmics may have additive effects in slowing cardiac conduction (table 5). Phenothiazin has many cardiac side effects owing to its proarhythmic and antiarhythmic properties. It therefore has rate limiting properties on one hand and can also trigger life-threatening arrhythmias particularly in vulnerable patients with background cardiac illnesses such as ischaemic heart disease, arrhythmias, and heart failure. Gabapentin and lamotrigine, the relatively newer antiepileptic agents, have a favourable pharmacokinetic profile compared with other antiepileptic drugs. In general, they have no significant cardiac effects, few other side effects, and are better tolerated than other antiepileptic drugs.


22 Buckley NA, Whyte IM, Dawson AH. Cardiototoxicity more common in thioridazine overdose than with other neuroleptics. Clinical Toxicology 1995;33:199–204.


Heart and mind: (2) psychotropic and cardiovascular therapeutics

S U Shah, Z Iqbal, A White and S White

doi: 10.1136/pgmj.2003.015230

Updated information and services can be found at:
http://pmj.bmj.com/content/81/951/33

These include:

References
This article cites 53 articles, 4 of which you can access for free at:
http://pmj.bmj.com/content/81/951/33#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/