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# Antidepressant poisoning

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Antidepressants are involved in about one in five cases of overdose. They cause significant morbidity and are the second most common cause of fatal drug overdose in the UK.

## Tricyclic antidepressants

Tricyclic antidepressants account for most deaths from antidepressant overdose. Dosulepin and amitriptyline are particularly toxic. The mechanisms of toxicity are summarised in Table 1.

### *Clinical features*

The clinical features of tricyclic antidepressants include anticholinergic, cardiovascular and neurological effects.

*Anticholinergic effects.* Serious anticholinergic effects that may be associated with poisoning include ileus, urinary retention, confusion, and postural hypertension.

**Table 1. Mechanisms of toxicity of tricyclic antidepressants** (adapted from Ref 1).

- Sodium channel blockade (membrane stabilising action or 'quinidine-like' effect)
- Anticholinergic activity at autonomic nerve endings and in the brain
- Inhibition of norepinephrine reuptake at nerve terminals
- Vascular α-adrenergic blockade

*Cardiovascular effects.* Tricyclics retard phase 0 cardiac depolarisation by inhibiting sodium channels. The delay in propagation of depolarisation in the atrioventricular (AV) node, His-Purkinje fibres and ventricular myocardium leads to prolongation of the PR and QRS interval (Fig 1). A right bundle branch block pattern may be seen, but second- or third-degree AV block is uncommon. In more severe poisoning, ventricular tachycardia can occur, especially in those with marked QRS prolongation or hypotension, and may degenerate into ventricular fibrillation.

Tricyclic antidepressants slow repolarisation and prolong the QT interval, predisposing to *torsade de pointes*. However this is uncommon; sinus tachycardia is usually the underlying rhythm in tricyclic poisoning, whereas *torsade de pointes* is a bradycardia or pause-dependent arrhythmia.

Hypotension results from a combination of diminished myocardial contractility and peripheral resistance. Refractory hypotension is a common cause of death.

*Central nervous system effects.* Severe neurological features include drowsiness, ataxia, hypertonia and hyperreflexia with extensor plantar responses. Respiratory depression and deepening coma may occur, especially when other CNS depressant substances have also been ingested. Severe agitation and delirium may be present, particularly during recovery.

Convulsions occur in more than 5% of cases and are more likely if there is QRS prolongation. Seizures may exacerbate hypotension and trigger ventricular arrhythmias by worsening acidosis and hypoxia.

### *Investigations*

1 A *12-lead ECG* is essential. Prolongation of QRS interval predicts seizures (QRS >0.10 sec) and ventricular arrhythmias (QRS >0.16 sec).[2] A terminal R wave above 3 mm in lead aVR, or an R wave/S wave ratio of over 1.4 may be a better predictor than QRS

duration but is not commonly used.[3]

2 *Arterial blood gas analysis:* metabolic acidosis is the most common abnormality; hypoxia and other features of respiratory depression may also be detected.

3 *Electrolytes:* it is important to detect and treat hypokalaemia.

Measurement of plasma drug concentration is clinically not useful and is less predictive of complications than QRS duration.

### Management

Assessment and management of tricyclic antidepressant overdose are summarised in Tables 2 and 3, respectively.

*Cardiac monitoring.* Asymptomatic patients should have continuous cardiac monitoring for at least six hours. Patients with signs of toxicity should be monitored until these disappear and the ECG has been normal for 12 hours. Late arrhythmias do not occur once cardiovascular toxicity has resolved.

*Gut decontamination.* Gut decontamination reduces systemic drug absorption, but there is no evidence that this improves clinical outcome. The current consensus is that activated charcoal should be given if a potentially toxic amount has been taken within one hour[4] and repeated after two hours if central features are present.[5] Gastric lavage should be considered only if a potentially life-threatening dose has been ingested within one hour,[6] although there is no clinical evidence of benefit. The airway must be adequately protected. Hypoxia is likely to occur during the procedure; arrhythmias are a significant risk both during the procedure and for two hours afterwards.

*Sodium bicarbonate.* Hypertonic sodium bicarbonate ($NaHCO_3$) is effective in treating QRS prolongation, ventricular arrhythmias and hypotension associated with tricyclic toxicity.[7] Alkalinisation increases plasma protein binding and reduces myocardial binding and cardiotoxicity, while the extracellular sodium load also improves sodium channel function. Intravenous $NaHCO_3$ 8.4% in a dose of 50 ml should be given over 15–20 minutes and can be repeated until the ECG normalises or the blood pH is greater than 7.45. Excessive alkalaemia (pH >7.55) may precipitate ventricular arrhythmias.

*Arrhythmias.* Administration of $NaHCO_3$ and correction of acidosis, hypoxia and electrolyte abnormalities are the mainstay of treatment. Antiarrhythmic agents may worsen arrhythmias by further blocking sodium channels (class I) or delaying cardiac repolarisation (class III). Beta-blockers can sometimes be useful but may exacerbate hypotension. Magnesium sulphate has been used in refractory ventricular fibrillation.

Following cardiac arrest, recovery has been reported after several hours of cardiopulmonary resuscitation.

*Hypotension.* Hypotension may respond to simple measures such as raising the foot of the bed and intravenous plasma expanders. Inotropic support may be needed for protracted hypotension and glucagon has been used successfully.[8] Adrenergic agonists are effective but may worsen arrhythmias. Intra-aortic balloon pumping may be used in treating refractory hypotension.

*Convulsions.* Intravenous diazepam or lorazepam should be used to control

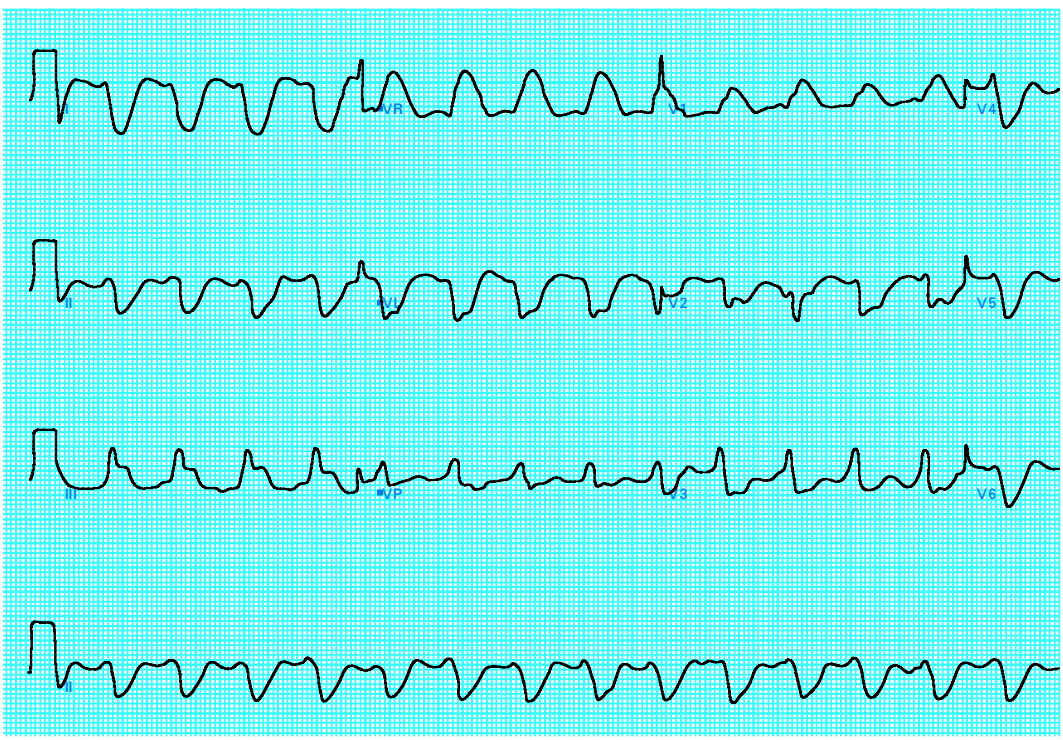


**Fig 1. ECG in severe tricyclic antidepressant poisoning demonstrating widening of the QRS complex.**

convulsions, avoiding phenytoin which worsens sodium channel blockade and may exacerbate arrhythmias. Anaesthesia, neuromuscular paralysis and mechanical ventilation should be considered for refractory seizures.

*Agitation.* Drug-induced agitation and psychosis are common and may require high doses of benzodiazepines. Major tranquillisers should be avoided since these may exacerbate hypotension, arrhythmias and fits.

*Drug elimination techniques.* Haemodialysis, haemoperfusion and forced diuresis do not increase clearance due to the large volume of distribution of tricyclic antidepressants. Drug-specific ovine antibody Fab fragments have given promising results but are not yet routinely available.[9]

**Table 2. Assessment of tricyclic antidepressant overdose.**[1]

- Airway, breathing and circulation
- Intravenous access
- Cardiac monitoring
- ECG
- U&Es
- Arterial blood gas analysis

U&E = urea and electrolyte.

## Selective serotonin re-uptake inhibitors

The use of selective serotonin reuptake inhibitors (SSRIs) in drug overdose has increased markedly in line with their increased prescribing. They are safer than tricyclics in overdose, but occasionally cause significant toxicity. Nausea, vomiting and drowsiness are the most common features, but convulsions, hypotension, respiratory depression and ECG abnormalities can occur.[10] Citalopram may cause prolongation of the QT interval and QRS complex.

The serotonin syndrome[11] (Table 4) occurs occasionally. Patients taking a combination of an SSRI and tricyclic antidepressant or monoamine oxidase inhibitor (MAOI) are at particular risk.

### *Management*

Patients should not be discharged from hospital until six hours has elapsed since overdose because complications may develop within this period. Those who develop convulsions should be treated with a benzodiazepine and have their renal function and creatine kinase monitored.

**Table 3. Management of tricyclic antidepressant overdose.**[1]

| | |
|---|---|
| Gastric decontamination (within 1 hour) | |
| Correct | Hypoxia<br>Acidosis<br>Electrolyte abnormalities |
| Hypertonic $NaHCO_3$ (50 ml of 8.4%) | If any of the following is present:<br>• acidosis<br>• widened QRS, especially if >0.16 sec<br>• arrhythmias<br>• hypotension |
| Arrhythmias | Give $NaHCO_3$ as above<br>Avoid antiarrhythmic drugs especially class IA, IC, III<br>Correct hypoxia, acidosis, electrolyte abnormalities |
| Hypotension | $NaHCO_3$<br>Intravenous fluids<br>Glucagon<br>Consider inotropes (eg norepinephrine for non-responders)<br>Intra-aortic balloon pumping for refractory hypotension |
| Convulsions | Airway protection<br>Benzodiazepines |
| Cardiac arrest | Continue CPR<br>Magnesium for refractory VF |

CPR = cardiopulmonary resuscitation; $NaHCO_3$ = sodium bicarbonate; VF = ventricular fibrillation.

## Newer antidepressants

### *Mirtazapine*

Mirtazapine has presynaptic alpha$_2$-antagonist and $H_1$-receptor antagonist activity. Limited information is available, but it appears relatively safe in overdose, its principal effect being sedation. It is unlikely to cause convulsions.

### *Reboxetine*

The selective noradrenaline reuptake inhibitor reboxetine is thought to be relatively safe in overdose but human data are scarce. Hypotension, tachycardia and urinary retention may occur.

### *Venlafaxine*

Use of the selective serotonin and noradrenaline reuptake inhibitor venlafaxine is increasing. Overdose causes sedation and occasionally convulsions. QT interval prolongation has been reported.

### *Trazodone*

Overdose of trazodone, an atypical antidepressant, commonly causes drowsiness, nausea and vomiting. Rare complications are hypotension, respiratory failure, hyponatraemia, convulsions and prolongation of the QT interval leading to *torsade de pointes* and cardiac arrest.

## Monoamine oxidase inhibitors

After an MAOI overdose there is an asymptomatic period lasting up to 12 hours. This is followed by sympathetic and neuromuscular hyperactivity characterised by agitation, tremor, hyperreflexia, hyperthermia, rigidity and seizures. Finally, central nervous system depression and cardiovascular collapse may occur.

Moclobemide, a reversible MAOI,

**Table 4. Clinical features of the serotonin syndrome.**

| | |
|---|---|
| Altered mental status | Agitation, delirium, hallucinations, drowsiness, coma) |
| Autonomic instability | Tachycardia, hyperpyrexia, hypertension or hypotension |
| Neuromuscular hyperactivity | Shivering, tremor, teeth grinding, myoclonus, hyperreflexia |
| Flushing | |
| Gastrointestinal features | Diarrhoea, vomiting |
| Rhabdomyolysis and renal failure | |
| Coagulopathy | |

appears less toxic in overdose. It may cause vomiting, blood pressure changes, tachycardia and drowsiness.

All MAOIs may give rise to the serotonin syndrome when taken in combination with an SSRI or clomipramine.

### *Management*

Activated charcoal should be given by mouth if the patient presents within one hour. Convulsions, agitation and muscular spasm should be managed with benzodiazepines. Cooling measures and dantrolene can be used for hyperthermia. For persistent hypertension, a short-acting beta-blocker such as esmolol or metoprolol may be used.

## Lithium

Lithium is mainly used in the treatment of bipolar depressive illness, usually as a slow-release preparation of lithium carbonate. It has a low therapeutic index and needs regular monitoring. Lithium is cleared from the body by the kidney (half-life 18–36 hours); it is filtered at the glomerulus and reabsorbed in the proximal tubule and loop of Henle.

Lithium toxicity[12] may be provoked by excessive dosing, dehydration or by drugs that affect lithium excretion. Important examples are non-steroidal anti-inflammatory agents, diuretics and angiotensin-converting enzyme inhibitors. Lithium-induced neurotoxicity may occur at lower plasma concentrations in the presence of SSRIs, antidepressants, carbamazepine, phenytoin, methyldopa and antipsychotic drugs.

It is important to differentiate the three types of lithium toxicity because the type affects the interpretation of plasma lithium concentrations, prognosis and management:

- acute (ie overdose taken by patients not previously receiving lithium)
- acute-on-chronic (ie acute overdose by patients already on lithium treatment), or
- chronic.

### *Clinical features*

These are summarised in Table 5. The correlation between serum lithium concentration and the development of symptoms of toxicity is poor.[13] Single acute overdoses usually produce only mild symptoms, despite high plasma lithium concentrations. Patients with chronic or acute-on-chronic toxicity commonly develop symptoms at lower plasma lithium concentrations because tissue concentrations are higher as a result of more complete distribution in body water.

### *Investigations*

Plasma lithium concentration should be measured immediately in patients with symptoms or suspected chronic toxicity. Measurement should be delayed for six hours in asymptomatic patients following acute overdose. If severe poisoning is present or a sustained-release preparation has been taken, the measurement should be repeated every 6–12 hours until the level begins to fall. The therapeutic range for lithium is typically 0.4–1.2 mmol/l but may vary between laboratories. The ECG should be monitored in symptomatic patients.

### *Management*

Hydration and correction of electrolyte imbalances are important. Hypotension and fits should be treated conventionally.

*Gut decontamination*. Activated charcoal is not useful. Gastric lavage may be considered if the patient presents within one hour of a potentially life-threatening overdose. Sodium polystyrene sulphonate and whole-bowel irrigation reduce lithium absorption, but there is no evidence that clinical outcome is affected by any of these interventions.

*Elimination.* Haemodialysis is the treatment of choice in serious lithium intoxication; it is indicated when severe clinical

**Table 5. Clinical features of lithium toxicity.**

| | Poisoning | |
|---|---|---|
| **System** | **Mild/moderate** | **Severe** |
| Gastrointestinal | Nausea, vomiting, diarrhoea | |
| Neurological | Apathy, lethargy, drowsiness, tremor, muscle fasciculations, blurred vision | Myoclonic movements, ataxia, chorea, confusion, mania, hyper reflexia, agitation, stupor, seizures, coma |
| Cardiovascular | QT prolongation | Arrhythmias (*torsade de pointes*, sinus arrest asystole), hypotension |
| Renal/metabolic | Polyuria, hypernatraemia | Acute renal failure |
| Respiratory | | Adult respiratory distress syndrome |
| Haematological | Neutrophil leucocytosis | |

effects are associated with a high plasma lithium concentration. Haemodialysis should be used in all patients with severe neurotoxicity, but patients with lithium concentrations below 2.5 mmol/l or those without neurotoxicity and concentrations below 4.0 mmol/l can usually be treated conservatively. Following dialysis, a rebound rise in serum lithium concentration may occur due to redistribution from tissues. High-volume continuous venovenous haemofiltration has also been used successfully and may avoid haemodynamic instability and rebound increases in lithium concentration after dialysis.[14,15]

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## Key Points

**Overdose with antidepressants is common and may cause significant morbidity, particularly when tricyclics, monoamine oxidase inhibitors or lithium are involved**

**Patients admitted with tricyclic antidepressant poisoning must have continuous cardiac monitoring. Sodium bicarbonate is important for preventing and treating complications**

**Selective serotonin reuptake inhibitors are relatively safe in overdose but occasionally cause convulsions, ECG abnormalities and the serotonin syndrome**

**Newer antidepressants are increasingly used in self-poisoning. Although safer than tricyclics in overdose, the available evidence is limited. Venlafaxine is commonly used and may cause convulsions**

**Lithium has a narrow therapeutic ratio and chronic toxicity may arise from drug interactions. Haemodialysis is indicated for patients with severe effects, especially neurotoxicity. Rebound increase in lithium may occur following haemodialysis**

**KEY WORDS: antidepressants, lithium, mirtazapine, monoamine oxidase inhibitors, overdose, poisoning, raboxetine, selective serotonin reuptake inhibitors, trazodone, tricyclic antidepressants, venlafaxine**