Guidelines in Emergency Medicine Network (GEMNet): guideline for the management of tricyclic antidepressant overdose

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ABSTRACT

The Guidelines in Emergency Medicine Network (GEMNet) has been created to promote best medical practice in a range of conditions presenting to emergency departments (EDs) in the UK.

This guideline presents a summary of the best available evidence to guide the management of adult patients who present to the ED following an overdose of tricyclic antidepressant agents (TCA).

The document has been developed following discussion among emergency physicians to decide which topics would benefit from the development of clinical guidelines.

The document is intended as a guideline for use in the ED by emergency physicians and is based on the review of the best existing evidence for the diagnostic tools and treatments used in this setting.

The document is summarised as a clinical decision support guideline that has been presented as an easy to follow algorithm.

The intention is for each guideline to be updated and reviewed as further evidence becomes available. The formal revision date has been set at 5 years from publication, although the guideline is subject to continuous informal review.

INTRODUCTION

Responsibility for development

This document has been developed in response to a perceived need to improve clinical effectiveness for care in this field. The emergency department (ED) at the Manchester Royal Infirmary has been undertaking primary and secondary research for a number of years to achieve this aim. The intention is to distil this information into practical advice for clinicians working in the department. The information is presented in the form of clinical decision support guidelines, available on the ‘shop floor’ in the form of a Clinical Decision Support Manual and on individual A4 sized forms.

Departmental consultants have considered clinical conditions that may benefit from evidence-based guidelines and, following discussion with other clinical staff, have compiled a list of topics that included tricyclic antidepressant (TCA) overdose.

The Guideline Working Group

A Guideline Working Group met to discuss this condition and decide on the clinical questions, consider the evidence available and develop the recommendations. The group process ensured that the Working Group had access to the relevant information and the required resources in order to develop in a constructive manner.

The guideline has been developed in accordance with the principles described by the National Institute for Health and Clinical Excellence guideline development methods.

TOPIC INTRODUCTION

TCAs are prescribed in the UK for problems including depression, anxiety and chronic pain. Recent recommendations have meant that prescribing practices are changing and the availability of TCA is declining. Despite this, TCA overdose still accounts for up to 18% of all poisoning deaths in the UK. The toxicity of the TCA coupled with the high-risk patient group who have access to TCAs means that self-poisoning episodes are more likely to be fatal. In the UK in 2005 there were 272 deaths related to TCA overdose.

Patients presenting to the ED with significant overdose pose difficult management issues. TCAs block α-adrenergic receptors and have anticholinergic effects. This may lead to cardiovascular effects including sinus tachycardia, cardiac conduction abnormalities, vasodilation, arrhythmias, hypotension and asystole. The anticholinergic effects of TCAs may also lead to dry mouth, blurred vision, dilated pupils, hyperthermia and delayed gastric emptying. Intestinal obstruction and perforation have been reported, as has pancreatitis. Finally, TCAs exert a number of effects on the central nervous system which may lead to drowsiness, coma, respiratory depression, seizures and delirium. Ophthalmoplegia has also been reported. Many patients require intensive care support or hospital admission.

To date, the Toxbase database provided by the National Poisons Information Service has been the initial portal for treatment advice in TCA overdose. This guideline does not aim to replace previous advice but to present a complementary structured guideline and evidence-based flowchart to aid the decision-making process for these patients within the ED. The document is presented as a series of clinical questions which have been answered using the previously described Best BETs methodology.

The aim of the guideline is to summarise the evidence supporting the various therapeutic options that have been advocated in the management of TCA overdose within the ED. It is hoped that this will help to optimise and standardise the standard of care that may be delivered to this patient group.
SCOPE OF THE GUIDELINE

This guideline encompasses adult patients (>16 years of age) presenting to the ED with suspected lone TCA overdose. The key aspects of this is designed to include are initial assessment, decontamination, active management and disposition of the patient from the ED. The initial assessment and management recommendations can be followed using resources available in any UK ED. Disposition may vary depending on local resources, but the guideline may be adapted as appropriate.

This document does not provide guidance regarding patients aged <16 years, patients with multiple drug overdose and those patients who present in cardiac arrest. The use of experimental or limited availability treatments such as extracorporeal mandatory oxygenation (ECMO) is also excluded because of limited availability throughout the country.

METHODOLOGY

This guideline was developed using a novel methodology that has recently been used in cardiothoracic surgery. Many guidelines perform a single systematic review of the literature in order to answer all of the relevant clinical questions. To maximise sensitivity, we performed a separate short-cut systematic review of the literature for each clinical question identified.

Guideline development was structured into several stages. Initially the two lead guideline developers (TB and RB) met to discuss the scope of the guideline and to identify all clinical questions that may have been relevant. In order to answer the clinical questions identified, we performed a series of structured short-cut systematic reviews (Best Evidence Topic Summaries, BETs), the principles of which have been previously described. Where relevant BETs had already been created, the search strategies were checked and updated when necessary. Literature searching was standardised for each short-cut systematic review by using custom-designed filters for each element of the search (Appendix 2). Relevant papers are summarised in tabulated format in Appendix 1.

Having gathered and collated the evidence for each clinical question, the principal guideline developers met to create a series of guideline recommendations which were used to create an evidence-based flowchart (Figure 1). Following consultation with the senior author (KMJ), modifications were made before the final guideline was agreed upon.

Levels of evidence and grading of recommendations

Studies included in this guideline were graded for level of evidence according to previously accepted definitions. In summary, level 1 evidence comes from well-designed randomised controlled trials (RCTs), level 2 evidence from large cohort studies or poorly designed RCTs, level 3 evidence from small cohort studies or case–control studies and level 4 evidence from experimental studies, case series or case studies. The suffix ‘a’ implies that evidence at this level is from systematic review or meta-analysis, whereas the suffix ‘b’ implies that the evidence is from original research.

The recommendations that have been made were graded according to the level of evidence upon which they were based:

- **Grade A**: Based upon multiple level 1a or 1b papers.
- **Grade B**: Based upon individual level 1a or 1b papers or multiple level 2a or 2b papers.
- **Grade C**: Based upon individual level 2a or 2b papers or multiple level 3a or 3b papers.
- **Grade D**: Based upon individual level 3a or 3b papers or level 4 papers.
- **Grade E**: Based on consensus guidelines or studies of expert opinion.

Definition of TCA overdose

For the purposes of this guideline, TCA overdose is defined as suspected deliberate or accidental ingestion of TCA at above the recommended therapeutic dose.

SUMMARY OF RECOMMENDATIONS

Airway protection

- Patients with Glasgow Coma Score (GCS) ≤8 should undergo rapid sequence induction at the earliest opportunity (Grade C).
- Some patients with GCS >8 may also need intubation, particularly in the presence of airway compromise, hypventilation or refractory seizures (Grade C).
- Benzodiazepines may be considered to control agitation following TCA overdose (Grade E).

Gastric decontamination

- Activated charcoal may be considered for use within 1 h of TCA ingestion, but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use (Grade D).
- Multiple dose activated charcoal should not be considered (Grade D).
- Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 h of ingestion and the airway is protected (Grade D).

Initial assessment

- An ECG should be recorded at presentation to the ED following TCA overdose (Grade B).
- The ECG should be used to risk stratify patients with TCA overdose and to guide subsequent therapy (Grade B).
- Serial ECG recordings should be examined for the presence of QRS prolongation (>100 ms), QTc prolongation (>450 ms) and R/S ratio >0.7 in lead aVR. These changes identify patients at high risk of developing complications following TCA overdose (Grade B).

Blood pH for risk stratification

- Blood gas analysis is an important part of the initial assessment and monitoring of patients who have taken a TCA overdose (Grade E).
- Venous sampling for blood gas analysis is an acceptable alternative to arterial sampling unless hypoxia or hypventilation are suspected (Grade D).

Treatment of haemodynamic instability

- A bolus of intravenous fluids should be considered as first-line therapy to treat hypotension induced by TCA overdose (Grade D).
- Sodium bicarbonate is indicated for the treatment of dysrhythmias or hypotension associated with TCA overdose (Grade C).
- Sodium bicarbonate may be considered for the treatment of QRS prolongation (>100 ms) associated with TCA overdose (Grade E).
- The treatment of dysrhythmias or hypotension should include alkalinisation to a serum pH of 7.45–7.55 (Grade E).
- Vasopressors should be used for hypotension following TCA overdose that has not responded to initial treatment (including sodium bicarbonate and intravenous fluids) (Grade D).
Epinephrine may be superior to norepinephrine for treating refractory hypotension and preventing arrhythmias (Grade D).

It is not unreasonable to administer 10 mg intravenous glucagon to treat life-threatening hypotension or arrhythmias refractory to other measures (Grade D).

Magnesium sulphate may be considered for the treatment of TCA-induced dysrhythmias when other treatments have been unsuccessful (Grade D).

Lipid emulsion may be considered for treatment of life-threatening toxicity following TCA overdose that is refractory to other measures (Grade D).

Management of seizures

Phenytoin should be avoided in patients with TCA overdose (Grade D).

Benzodiazepines should be used to control seizures following TCA overdose (Grade E).

Observation of asymptomatic patients

Following TCA overdose, asymptomatic stable patients with no significant ECG abnormalities 6 h after ingestion may be safely discharged (Grade B).

EVIDENCE FOR RECOMMENDATIONS

Below are summaries of the short-cut systematic reviews used to establish the recommendations for this guideline. The three-part question and search details are presented with comments and clinical bottom line. The search strategies are summarised and can be found in full in the appendix.

Airway protection

a. Assessing the need for intubation following TCA overdose in patients with reduced level of consciousness.
b. Can sedation be safely used in agitated patients with TCA overdose?

Assessing the need for intubation following TCA overdose in patients with reduced level of consciousness

Three-part question

In (adult patients who present to the ED following a psychotropic drug overdose with a reduced level of consciousness) does (endotracheal intubation vs standard treatment alone) lead to (fewer respiratory complications, reduced mortality and reduced length of hospital stay)?

Search strategy

Ovid Medline 1950–2008 May week 2
Ovid Embase 1980–2008 week 21
(Overdose filter) AND (Intubation filter) AND (Unconsciousness filter) limit to humans and English language.

Search outcome

Sixty-two papers were identified in Medline and 159 in Embase. Six were relevant to the three-part question (table A1).

Comments

In total we identified five retrospective analyses of patients who had been admitted following psychotropic drug overdoses and one prospective diagnostic cohort study that investigated the association between Matthew-Lawson coma grade and serious complications following TCA overdose. Although the studies have significant weaknesses, a strong correlation has consistently been shown between level of consciousness and the development of serious complications including death, hypventilation and aspiration pneumonia following drug overdose.

Of interest, both Hulten et al28 and Emerman et al29 showed that TCA drug levels are of little use for predicting complications, especially when coma grade and QRS width were taken into account. Furthermore, it seems that level of consciousness is a stronger independent predictor of complications than QRS width. The evidence strongly suggests that patients with GCS ≤8 should undergo intubation at an early stage in the ED. Results from the retrospective study by Liisanantti et al30 suggest that intubation at the earliest possible opportunity may reduce complication rates. Furthermore, in the study by Emerman et al, GCS ≤8 was only 86.5% sensitive for prediction of hypventilation or loss of protective airway reflexes.29 Thus, intubation may still be necessary for some patients with GCS >8 from a pragmatic patient safety viewpoint.

Clinical bottom line

Patients who present to the ED following psychotropic drug overdose with GCS ≤8 should undergo intubation at the earliest opportunity. Some patients with GCS >8 may also need intubation.

Recommendations

Patients with GCS ≤8 should undergo rapid sequence induction at the earliest opportunity (Grade C).

Some patients with GCS >8 may also need intubation, particularly in the presence of airway compromise, hypventilation or refractory seizures (Grade C).

Can sedation be safely used in agitated patients with TCA overdose?

Three-part question

In (agitated adult patients who present to the ED after an overdose of TCA drugs) does (the use of sedative agents) lead to (an acceptably low rate of pulmonary aspiration)?

Search strategy

Ovid MEDLINE 1950–2008 June week 1
Ovid EMBASE 1980–2008 week 24
(TCA filter) AND (Overdose filter) AND ((Benzodiazepine filter) OR ((Sedation filter) AND (Aspiration filter))) LIMIT to humans and English language.

Search outcome

One thousand seven hundred and eighty-seven papers were identified (194 in Medline and 1593 in Embase). None were relevant to the three-part question.

Comments

There is no evidence of harm when intravenous sedation is administered in agitated patients who have taken an overdose of TCAs. The National Poisons Information Service recommends the use of benzodiazepines to control delirium in this situation.31 Because TCAs are known to delay gastric emptying and many patients who have taken an overdose have also consumed a large

Clinical bottom line

There is no evidence of harm when sedating agitated patients following TCA overdose. National Poisons Information Service guidance advocates the use of benzodiazepines to control delirium in this situation. Caution should be exercised in view of the potential risks of pulmonary aspiration.
amount of alcohol, it would be advisable to exercise caution when sedating these patients. When there is doubt regarding a patient’s protective airway reflexes, endotracheal intubation may be necessary. However, there is no evidence to suggest that sedation should not be attempted in these patients.

**Recommendation**
- Benzodiazepines may be considered to control agitation following TCA overdose (Grade E).

**Gut decontamination**
- Activated charcoal.
- Multiple dose activated charcoal.
- Gastric lavage.

**Activated charcoal**

**Three-part question**
In (adults who have taken a TCA overdose) is (activated charcoal) effective at (reducing drug absorption and reducing complication rates)?

A short-cut systematic review to answer this three-part question has been documented within the literature. This was updated.

**Search strategy**
- Ovid Medline 1950–2008 May week 3
- Ovid Embase 1980–2008 week 22
  (TCA filter) AND (Overdose filter) AND (Charcoal filter) LIMIT to Humans and English language.

**Search outcome**
Sixty-seven papers were found in Medline and 125 in Embase. Six were relevant to the three-part question. One study was excluded due to insufficient quality (table AIII).

**Comments**
Experimental volunteer studies have consistently shown that administration of activated charcoal to patients who have ingested TCA within 1 h leads to a reduction in TCA absorption and bioavailability. However, it is not possible to extrapolate these results to the clinical situation of patients with TCA overdose. Larger doses of TCA may lead to delayed gastric emptying, which may alter the observed effects of activated charcoal. Further, the risk of pulmonary aspiration may be increased.

One small observational study showed that time to charcoal administration, caution should be exercised before prescribing activated charcoal in this patient group.

**Recommendation**
- Activated charcoal may be considered for use within 1 h of TCA ingestion but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use (Grade D).

**Multiple dose activated charcoal**

**Three-part question**
In (TCA overdose) is (Multiple dose Activated charcoal better than single dose Activated charcoal) at (reducing toxicity and improving clinical outcome)?

**Search strategy**
- Ovid Medline 1950–2008 May week 3
- Ovid Embase 1980–2008 week 22
  (TCA filter) AND (Overdose filter) AND (Charcoal filter) LIMIT to Humans and English language.

**Search outcome**
Sixty-seven papers were found in Medline and 125 in Embase. Six were relevant to the three-part question (table AIV). One study was excluded due to insuffcient quality.

**Multiple dose charcoal appears to increase elimination.**

**Comment(s)**
Multiple dose charcoal appears to increase elimination. However, the level of evidence is poor due to the use of volunteer studies. These studies are difficult to apply to the clinical setting of the ED as the patients did not receive the overdose amount and were treated more quickly than in the clinical setting.

The effect of multiple dose charcoal on clinical outcomes and complications such as arrhythmias and hypotension have not been studied, therefore the effect of multiple dose charcoal in the clinical setting cannot truly be assessed as the measurements are not clinically relevant. Studies used in the clinical setting have small numbers of patients. There is a need for larger studies in the clinical setting.

**Clinical bottom line**

There is no convincing clinical evidence that multiple dose activated charcoal reduces toxicity and improves clinical outcome.

**Recommendation**
- Multiple dose activated charcoal should not be considered (Grade D).

**Gastric lavage**

**Three-part question**
In (TCA overdose) which (method of gastric decontamination) is better at (reducing toxicity and improving clinical outcome)?

**Search strategy**
- Medline 1950–2008 June week 1
- Embase 1980–2008 week 23
  (TCA filter) AND (Overdose filter) AND (Lavage filter) LIMIT to Humans and English language.

**Search outcome**
Fifty-eight papers were identified in Medline and 141 in Embase. Two papers were directly relevant to the three-part question (table AIV).

**Comment(s)**
There seems to be no significant difference between gastric lavage and activated charcoal. Kulig et al showed that gastric lavage...
improved clinical outcomes after drug overdose (not specifically TCA overdose) when performed within 1 h compared with no treatment. The European toxicologists’ consensus statement is, at least in part, based upon this.43 One small study of 15 consecutive patients who presented to the ED with evidence of antidepressant overdose and underwent gastric lavage showed that, where estimated time of ingestion was available, none of the patients received gastric lavage within 1 h of ingestion. The mean time to delivery of gastric lavage was 6 h. Furthermore, a mean of only 8.7% of the estimated dose ingested was recovered.44

Clinical bottom line

There is no clinical evidence for the benefit of gastric lavage in TCA overdose. In a clinical setting, gastric lavage is unlikely to recover a clinically significant amount of antidepressant. Its use should only be considered in the context of a potentially life-threatening overdose with a protected airway where lavage can be delivered within 1 h of ingestion. Activated charcoal is less invasive and may be a preferable alternative in conscious patients.

Recommendation

▶ Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 h of ingestion and the airway is protected (Grade D).

Electrocardiography (ECG)

a. ECG versus serum drug level as a predictive tool.
b. ECG changes as predictors of severity of overdose.

ECG versus serum drug level as a predictive tool

Three-part question

In (TCA overdose) is the (ECG a greater predictor than serum drug level) at predicting (seizures and arrhythmias)?

Search strategy

Ovid Medline 2008 June week 1
Ovid Embase 2008 week 23
(TCA filter) AND (ECG filter) AND (Overdose filter).

Search outcome

Three hundred and eighty-eight papers were found (143 in Medline and 245 in Embase) including one systematic review that incorporated a meta-analysis of all other relevant studies that had been identified (table AV).

Comment(s)

The meta-analysis by Bailey et al demonstrates that ECG abnormalities are fairly good predictors of serious complications including death, seizures and ventricular arrhythmias. A QRS width >0.1 s would appear to be the strongest predictor of complications. Indeed, the wider the QRS complex the greater is the apparent risk of arrhythmias, with one group reporting a 50% incidence of arrhythmias when the QRS complex is >0.16 s in duration.45 However, the results of one study also suggest that QTc >450 ms predicts ventricular arrhythmias with reasonable sensitivity (78%) but lower specificity (56%) than QRS prolongation. Furthermore, one study demonstrated that R/S ratio >0.7 in lead aVR has a high positive predictive value (positive likelihood ratio 15.7) for predicting ventricular arrhythmias.

Importantly, it is recognised that the timing of ECG recording is important and serial recordings should be considered.

Clinical bottom line

QRS width >100 ms is a good predictor of complications following TCA overdose. QTc >430 ms and R/S ratio >0.7 in lead aVR may be useful for predicting complications.

Recommendation

▶ Serial ECG recordings should be examined for the presence of QRS prolongation (>100 ms), QTc prolongation (>430 ms) and R/S ratio >0.7 in lead aVR. These changes identify patients at high risk of developing complications following TCA overdose (Grade B).

Blood pH for risk stratification

a. pH versus ECG for risk stratification
b. Arterial or venous pH in conscious patients with TCA overdose

Arterial pH versus ECG for risk stratification

*Three-part question*

In (TCA overdose) is (ECG or blood PH) superior for (predicting seizures, reduced cardiovascular function and death)?

**Search strategy**

Ovid Medline 2008 June week 1
Ovid Embase 2008 week 23
(TCA filter) AND (ECG filter) AND (Overdose filter).

**Search outcome**

Three hundred and eighty-eight studies were identified (143 in Medline and 245 in Embase), none of which were relevant to the three-part question.

**Comment(s)**

There is no evidence that can assist in answering this question. The use of ECG as a predictor of complications in TCA overdose has been proved, but this has never been compared with the pH. More research is required in this area.

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**Clinical bottom line**

Venous blood gas analysis is an acceptable alternative to arterial blood gas analysis following TCA overdose unless hypoxia or hypoventilation are suspected.

**Recommendations**

- Blood gas analysis is an important part of the initial assessment and monitoring of patients who have taken a TCA overdose (Grade E).
- Venous sampling for blood gas analysis is an acceptable alternative to arterial sampling unless hypoxia or hypoventilation are suspected (Grade D).

**Adjunctive therapies**

- Intravenous fluids
- Sodium bicarbonate
- Vasopressors
- Glucagon
- Magnesium sulphate
- Lipid emulsion

**Intravenous fluids**

*Three-part question*

In (patients who have taken an overdose of TCAs and have developed hypotension) does (the administration of normal saline, colloid or no intravenous fluid) lead to (superior success in treating hypotension, quicker resolution of hypotension, fewer arrhythmias and quicker recovery)?

**Search strategy**

Ovid MEDLINE 1950–2008 June week 1
Ovid EMBASE 1980–2008 week 23
(TCA filter) AND (Hypotension filter) AND (Intravenous fluids filter) limit to English language.

**Search outcome**

One hundred and fifty-eight papers were identified (118 in Embase and 40 in Medline). None was relevant to the three-part question.

**Comment(s)**

There is no direct evidence for the use of intravenous fluids to treat hypotension in TCA overdose. However, the absence of evidence does not equate to evidence of absence. TCA-induced hypotension is likely to result from a combination of myocardial depression and reduced systemic vascular resistance. While intravenous fluids will not counter either of these effects, they may optimise cardiac preload thus improving the chances that a sufficient cardiac output will be achieved.

It is unlikely that a cautious fluid bolus will cause harm in this situation. Where concern exists about potential volume overload, invasive haemodynamic monitoring may be prudent.

The age-old argument of colloid versus crystalloid cannot be answered even for this well-defined situation. Colloid is believed to remain in the intravascular compartment for longer than
crystalloid. Of note, however, there is some evidence that sodium loading may be important in reversing TCA toxicity, which may lead the undecided clinician to favour saline infusion.

Clinical bottom line

There is no evidence within the literature that intravenous fluids counter TCA-induced hypotension. As there is a sound physiological rationale for their use, they may still be considered as a useful first-line treatment.

Recommendation

- A bolus of intravenous fluids should be considered as first-line therapy to treat hypotension induced by TCA overdose (Grade D).

Use of sodium bicarbonate for arrhythmias and hypotension

Three-part question

In (TCA overdose) does (sodium bicarbonate) improve (arrhythmias and hypotension)?

Search strategy

Ovid Medline 1950—2008 June week 1
Ovid Embase 1980—2008 week 23
(TCA filter) AND (Bicarbonate filter) limit to humans and English language.

Search outcome

Three hundred and fifty-seven papers were found (86 in Medline, 271 in Embase). One systematic review was relevant to the three-part question. While this incorporated all other relevant papers, the data were not suitable for meta-analysis. Four relevant papers are therefore tabulated (table AVII). Individual case reports are discussed but not tabulated. One survey of expert opinion is discussed.

Comment(s)

The use of sodium bicarbonate to treat the complications of TCA overdose is so well established in everyday clinical practice that it is perhaps surprising to discover that its use is not based upon high-level evidence. The evidence to supports its use is of a low level including only experimental animal studies, case reports and retrospective analyses.

In addition to the tabulated papers, the meta-analysis by Blackman et al cites a total of eight case reports where bicarbonate therapy has reportedly led to beneficial effects including resolution of QRS prolongation, recovery of hypotension, successful treatment of arrhythmias and spontaneous return of circulation following cardiac arrest. Furthermore, they cite a case series of 10 patients with QRS prolongation following TCA overdose in whom the QRS duration normalised during periods of hypocapnoea and worsened during periods of normocapnoea.

Given the available evidence, it would be prudent to use sodium bicarbonate to treat major toxicity following TCA overdose, including arrhythmias and refractory hypotension. Furthermore, as QRS prolongation is associated with a high risk of arrhythmias, the use of sodium bicarbonate would also be reasonable in this situation.

Most of the relevant studies provide few details regarding the target pH for successful alkalinisation therapy. However, in the largest published study the recommended regime was alkalinisation to a pH of 7.50—7.55. It would appear that the absence of acidosis need not preclude the use of sodium bicarbonate in this situation. The successful use of bicarbonate to treat TCA-induced arrhythmias has been reported in a patient with alkalosis. Notably, however, a case series of two patients reported the aggressive use of bicarbonate and hyperventilation in two patients with QRS prolongation and ventricular arrhythmias resulting in profound alkalosis (peak pH of 7.83 and 7.66, respectively) and death.

A 2003 survey asked 58 medical directors of United States Poisons Centres to specify the clinical situations in which they would recommend the use of sodium bicarbonate. 100% recommended sodium bicarbonate to treat QRS prolongation, 62% to treat hypotension, 53% to treat seizures, 51% to treat tachycardia, 16% to treat ventricular dysrhythmias and 3% to treat acidosis. 53% would use a QRS width threshold of 100 ms to recommend bicarbonate. Finally, 62% believed that the minimum target pH for alkalinisation should be 7.45 and 66% considered 7.55 to be the maximum pH target for alkalinisation therapy.

Current practice in many centres is to use 50—100 ml 8.4% (50 mmol) sodium bicarbonate; however, in stable patients the use of 500 ml 1.26% (75 mmol) sodium bicarbonate is safer in the event of extravasation.

Clinical bottom line

Sodium bicarbonate may be used to treat arrhythmias, hypotension and significant ECG abnormalities to a pH of 7.45—7.55 in TCA overdose even in the absence of initial acidosis.

Recommendations

- Sodium bicarbonate is indicated for the treatment of dysrhythmias or hypotension associated with TCA overdose (Grade C).
- Sodium bicarbonate may be considered for the treatment of QRS prolongation (>100 ms) associated with TCA overdose (Grade E).
- The treatment of dysrhythmias or hypotension should include alkalinisation to a serum pH of 7.45—7.55 (Grade E).

Vasopressors

Three-part question

In (TCA overdose with refractory hypotension) does the use of (catecholamines) improve (hypotension and survival)?

Search strategy

Ovid Medline 1950—2008 June week 1
Ovid Embase 1980—2008 week 23
(TCA filter) AND (Vasopressor filter) limit to English language.

Search outcome

Eight hundred and ten papers were identified (699 in Embase and 111 in Medline). Five were relevant to the three-part question (table AVIII).

Comment(s)

There is no published evidence of the effectiveness of catecholamines to treat refractory hypotension following TCA overdose. Perhaps importantly, however, there were no reports of harmful or potential pro-arrhythmic effects of catecholamines in this situation. Experimental studies in animals suggest that
epinephrine may be more effective than norepinephrine, with epinephrine potentially reducing some of the cardiotoxic effects of TCAs.

**Clinical bottom line**

There is no published evidence of benefit or harm with intravenous catecholamines following TCA overdose. They may be a useful adjunct in the treatment of refractory hypotension in this situation. Animal evidence suggests that epinephrine may be preferable to norepinephrine.

**Recommendations**

- Vasopressors should be used for hypotension following TCA overdose that has not responded to initial treatment (including sodium bicarbonate and intravenous fluids) (Grade D).
- Epinephrine may be superior to norepinephrine for treating refractory hypotension and preventing arrhythmias (Grade D).

**Glucagon**

**Three-part question**

In (overdose with TCAs) does (the addition of glucagon to standard treatments) improve (clinical outcome)?

**Search strategy**

Ovid Medline 1950–2008 June week 1
Ovid Embase 1980–2008 week 23

**Search details**

(TTCA filter) AND (Glucagon filter) limit to human and English language.

**Search outcome**

Eighty-four papers were identified (71 in Embase, 13 in Medline). Three papers were relevant to the three-part question (table AIX).

**Comment(s)**

There have been three case reports of the successful use of glucagon to treat refractory hypotension and arrhythmias and correct QRS prolongation following TCA overdose. In each of these cases the patient had received several other treatments, although the authors state that the improvement in clinical condition was temporarily related to glucagon administration. If it is effective, a 10 mg intravenous bolus may be necessary to elicit clinical improvement.

No reports of failure to respond to glucagon therapy were identified in the literature, although this is most probably attributable to reporting bias. Further research is necessary.

**Clinical bottom line**

It is reasonable to consider the use of magnesium sulphate for refractory dysrhythmias causing haemodynamic instability in the context of TCA overdose.

**Recommendation**

- Magnesium sulphate may be considered for the treatment of TCA-induced dysrhythmias when other treatments have been unsuccessful (Grade D).

**Lipid emulsion**

**Three-part question**

In (patients who have hypotension or circulatory collapse following TCA overdose) does (lipid emulsion or standard therapy alone) lead to (lower mortality and fewer complications)?

**Search strategy**

Ovid Medline 1950–2010 January week 1
Ovid Embase 1980–2010 week 2

(TCA filter) AND (Lipid Emulsion filter).

**Search outcome**

Twenty-three papers were identified including three relevant animal studies and one study in healthy volunteers (table AXI). There were no randomised controlled trials, cohort studies, case series or case reports of the use of lipid emulsion in the clinical environment.

**Comment(s)**

Lipid emulsion is a promising treatment for TCA overdose. TCAs are lipid soluble. Some have postulated that lipid emulsion
Lipid emulsion may be considered for treatment of life-threatening toxicity following TCA overdose that is refractory to other measures. Alternatively, lipid emulsion may work by enhancing free fatty acid metabolism. The only human data come from a volunteer study which demonstrated that lipid emulsion did not significantly alter TCA blood levels.

Our search also identified three animal studies. Harvey et al showed that lipid emulsion was superior to saline infusion for treatment of TCA-induced hypotension. The same group has also shown that lipid emulsion is superior to sodium bicarbonate for treatment of TCA-induced hypotension in rabbits. Finally, Yoav et al demonstrated that infusion of lipid emulsion resulted in lower mortality than saline infusion in TCA-intoxicated rats.

The Lipid Rescue website also contains one informal case report of the successful use of lipid emulsion to treat refractory ORS prolongation in an intubated patient following TCA overdose. The ECG changes resolved after 4 h and the patient recovered. In itself, this represents weak evidence for the efficacy of lipid emulsion in this situation. Furthermore, the patient developed haematuria after 4–5 h and haemoglobin could not be estimated because of the lipaemic sample. Interference with laboratory assays and hypertriglyceridaemia are important side effects of lipid emulsion.

However, given the evidence presented and in the absence of stronger evidence, it would be reasonable to administer lipid emulsion to a patient with serious life-threatening cardiotoxicity secondary to TCA overdose that is refractory to other measures.

**Clinical bottom line**

There is no evidence that lipid emulsion is of benefit as a standard treatment for TCA overdose in humans. However, given the results of three animal studies and a plausible physiological mechanism, lipid emulsion should be considered for life-threatening cardiotoxicity that is refractory to other measures following TCA overdose.

**Recommendation**

- Lipid emulsion may be considered for treatment of life-threatening toxicity following TCA overdose that is refractory to other measures (Grade D).

**Management of seizures**

- Phenytoin
- Benzodiazepines

**Phenytoin**

**Three-part question**

In (adult patients who develop seizures following TCA overdose) does the use of (benzodiazepines) lead to (safe and effective termination of seizures)?

**Search strategy**

- Ovid MEDLINE 1950–May 2008 week 24
- Ovid EMBASE 1980–2008 week 21
- (TCA filter) AND (Overdose filter) AND (Phenytoin filter) LIMIT to human and English language.

**Search outcome**

Seventy-three and forty-three papers were identified (186 in Medline and 1557 in Embase). None was relevant to the three-part question.

**Comment(s)**

There were no studies found that were relevant to the three-part question. Notably, there have been no reports of harmful interactions when benzodiazepines are used in TCA overdose. The National Poisons Information Service recommends the use of intravenous benzodiazepines to control seizures associated with TCA overdose.

**Clinical bottom line**

There is no evidence of benefit or harm when benzodiazepines are used to control seizures associated with TCA overdose. As there is no evidence of harm, the National Poisons Information Service guidance, which advocates the use of benzodiazepines in this situation, ought to be followed.
**Recommendation**

- Benzodiazepines should be used to control seizures following TCA overdose *(Grade E).*

**Observation of asymptomatic patients**

**Three-part question**

In (a clinically stable patient following TCA overdose) what (period of observation) enables (safe discharge)?

**Search strategy**

Ovid Medline 1950–2008 June week 1
Ovid Embase 1980–2008 week 24

(TCA filter) AND (Overdose filter) AND (Observation filter)

| Limit to Humans and English language.

**Search outcome**

Five hundred and ninety-two papers were identified (156 in Medline, 436 in Embase). Seven were relevant to the three-part question (table AXII).

**Comment(s)**

Late complications including cardiac arrhythmias have been reported to occur as long as several days after TCA overdose. However, in all of these cases there were significant

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**Figure 1** Evidence-based flowchart.

RSI, rapid sequence induction; TCA, tricyclic antidepressant.
Therapy notes

**Indications for rapid sequence induction (RSI)**
TCA overdose delays gastric emptying and may cause vomiting, increasing aspiration risk, particularly in patients with reduced level of consciousness. A low threshold for early intubation should be adopted and the need should be continually reassessed. It is imperative to ensure the availability of adequate expertise during rapid sequence induction.

**Gastric decontamination**
Activated charcoal may be considered for use within 1 h of TCA ingestion but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use. Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 h of ingestion and the airway is protected.

**Hypotension**
TCA overdose causes hypotension by reducing preload and afterload as well as direct effects on the myocardium. Optimising the preload may reverse hypotension. This may be achieved by head-down tilt and bolus of intravenous fluid. Sodium bicarbonate may reverse hypotension even in the absence of acidosis and is indicated if hypotension is persistent. If hypotension still persists, vasopressors/inotropes should be used. There is some evidence that epinephrine may be preferable to norepinephrine in this situation.

**Arrhythmias**
Administration of sodium bicarbonate, even in the patient without acidosis, may reverse TCA-induced arrhythmias. If arrhythmias are persistent, magnesium sulphate may be given, although there is limited available evidence for its efficacy.

**ECG abnormalities**
QRS prolongation (>0.10 s) and right axis deviation are associated with increased risk of cardiac arrhythmias. The use of sodium bicarbonate should be strongly considered in this situation.

**Sodium bicarbonate**
For life-threatening toxicity use 50—100 ml 8.4% sodium bicarbonate. The dose can be repeated with blood gas monitoring to a target pH of 7.45—7.55. For more stable patients, 500 ml 1.26% sodium bicarbonate carries less risk of skin necrosis in the event of extravasation.

**Refractory haemodynamic instability**
Use of glucagon, magnesium sulphate and lipid emulsion may be considered. Animal studies suggest that lipid emulsion (eg, Intralipid 20% 1.5 ml/kg over 1 min) may be a particularly promising therapy for the future, although evidence in humans is lacking.

**Seizures**
Prolonged seizures should be treated initially with benzodiazepines. Phenytoin should be avoided because of a possible interaction with TCAs. If there is no response to benzodiazepines, RSI should be considered.

**ECG monitoring**
ECG monitoring is essential for all patients at moderate/high risk. Serial 12-lead ECG recording is recommended in all patients to monitor for changes in QRS duration.
Stable patients with TCA overdose who show no sign of toxicity and have had no significant ECG abnormalities (including QRS < 0.10 s) for 6 h can be safely discharged.
Assessing the need for intubation in semiconscious patients presenting to the ED following psychotropic drug overdose

Table AI: Assessing the need for intubation in semiconscious patients presenting to the ED following psychotropic drug overdose

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study type</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al, 1993, Australia</td>
<td>Retrospective analysis</td>
<td>393 patients who presented to the ED with a history or evidence of overdose (a drug with or without a antidote) who had GCS documented at presentation</td>
<td>GCS ≤8/15 for prediction of intubation</td>
<td>67% of patients with GCS ≤8/15 were intubated. GCS ≤8/15 had sensitivity 90% (95% CI 81% to 99%) and specificity 95% (95% CI 93% to 97%) for prediction of intubation.</td>
<td>Relationship between GCS and intubation (logistic regression analysis)</td>
<td>Study only assesses what actually happened (whether patients were intubated or not). We do not know whether it was actually necessary to intubate the patients with GCS ≤8/15. No reporting of complications in semi-conscious patients who were/were not intubated</td>
</tr>
</tbody>
</table>

GEMNet guidelines

APPENDIX 1: RELEVANT PAPERS

73. Yanagawa Y, Sakamoto T, Okada Y. Recovery from a psychotropic drug overdose tends to depend on the time from ingestion to arrival, the Glasgow Coma Scale of documented at presentation no antidote) who had GCS ≤8/15 were intubated. OR 0.48 (95% CI 0.4 to 0.59), p < 0.0001 (ie, odds of intubation increase approximately twofold for every point decrease in GCS).
<table>
<thead>
<tr>
<th>Author date, country</th>
<th>Study type</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emerman et al, 1987, USA</td>
<td>Retrospective analysis</td>
<td>All 92 patients age ≥17 years who were admitted to Clevel and Metropolitan General Hospital with TCA overdose between 1975 and 1985</td>
<td>Association between GCS and complications (hypventilation, loss of protective airway reflexes, hypotension, seizures, haemodynamically significant arrhythmias or death)</td>
<td>Significant association (p&lt;0.001). GCS was significantly better than QRS interval (p&lt;0.001)</td>
<td>Retrospective. 38 patients had a mixed drug overdose (although subgroup analysis of patients with pure TCA overdose yielded similar results). Only 92 patients included over a 10-year period</td>
</tr>
<tr>
<td>Hulten et al, 1992, Sweden</td>
<td>Prospective diagnostic cohort study</td>
<td>67 patients ≥14 years from four centres with suspected TCA overdose. Excluded if mixed overdose detected and TCA was not the major cause of symptoms. Matthew-Lawson coma grade recorded</td>
<td>Matthew-Lawson coma grade ≥3 for prediction of serious complications (seizures, hypotension (systolic BP &lt;100 mmHg), arrhythmias, need for intubation)</td>
<td>Sensitivity 65%, specificity 94%</td>
<td>Matthew-Lawson coma grade not universally accepted for assessing conscious level (GCS not recorded). Need for intubation included as an outcome. Physicians may have decided to intubate on the basis of coma grade alone, thus introducing significant bias</td>
</tr>
<tr>
<td>Lisanantti et al, 2003, Finland</td>
<td>Retrospective analysis</td>
<td>257 patients admitted to ICU with self-poisoning of psychopharmaceutical drugs between November 1989 and October 2000. Classed as conscious (GCS 9–15) or unconscious (3–7) based on ‘approximate GCS’. 73 patients (28.4%) met criteria for aspiration pneumonia</td>
<td>Unconsciousness on discovery for prediction of aspiration pneumonia</td>
<td>OR 2.9 (95% CI 1.2 to 7.0)</td>
<td>Retrospective. ‘Approximate GCS’ used due to lack of universal use of GCS in Finland. Selection bias: only patients admitted to ICU included. GCS at time of initial contact with medical services not recorded in 20.6% of cases. Possible reporting bias — this centre may have noticed a particularly high rate of aspiration pneumonia in patients intubated late, prompting this analysis</td>
</tr>
<tr>
<td>Unverir et al, 2006, Turkey</td>
<td>Retrospective analysis</td>
<td>356 patients who presented to the ED with antidepressant ingestion between 1993 and 2004</td>
<td>Relationship between GCS and intubation rates</td>
<td>OR 34 (9.6%) patients were intubated. Low GCS was cited as the reason for intubation in 58.8% of cases. 100% of patients with GCS ≤8 were intubated compared with 5.6% of patients with GCS &gt;8</td>
<td>Retrospective. 'Obvious bias in outcome reporting: almost 60% of patients were intubated primarily because of low GCS. There was no attempt to correlate low GCS with incidence of complications</td>
</tr>
</tbody>
</table>

**Table AI** continued...
**Table AI**  
Continued

<table>
<thead>
<tr>
<th>Author date, country</th>
<th>Study type</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanagawa et al, 2006, Japan</td>
<td>Retrospective analysis</td>
<td>175 patients who were intubated following psychotropic drug overdose between January 2000 and December 2005. Patients were divided into an ‘early group’ (extubated within 2 days) and a late group (not extubated within 2 days)</td>
<td>Mean GCS (on arrival) in early and late groups</td>
<td>Logistic regression model for prediction of ‘late’ extubation (&gt;2 days)</td>
<td>Early group 6.2 (SE 0.2); late group 4.5 (SE 0.3); p = 0.001 GCS on arrival was an independent predictor of late extubation (OR 0.78, 95% CI 0.65 to 0.95)</td>
</tr>
<tr>
<td>Bosse et al, 1995, USA</td>
<td>PRCT</td>
<td>51 patients presenting to the ED with TCA overdose. Block randomisation to three groups: (1) 50g charcoal, 10oz magnesium citrate (2) Gastric lavage followed by 50 g charcoal and 10 oz magnesium citrate (3) 25 g charcoal, gastric lavage, followed by 25 g charcoal and 10 oz magnesium citrate</td>
<td>Mean serum TCA levels</td>
<td>No significant differences (p=0.797)</td>
<td>Block randomisation No sample size calculation – unknown power</td>
</tr>
<tr>
<td>Dawling et al, 1978, UK</td>
<td>Experimental, volunteer study, crossover design</td>
<td>6 fasted healthy volunteers given 75 mg nortriptyline, allocated to four groups on different occasions: (1) No treatment (2) 10 g Medicol after 30 min (3) 10 g Medicol after 2 h (4) 10 g Medicol after 4 h</td>
<td>Mean reduction in peak plasma nortriptyline concentrations</td>
<td>77% in group (2), 37% in group (3), 19% in group (4) (p=0.001)</td>
<td>Conducted in fasted volunteers. Small dose of nortriptyline</td>
</tr>
<tr>
<td>Hedges et al, 1986, USA</td>
<td>Prospective observational cohort</td>
<td>9 patients with TCA overdose who clinically required hospitalisation. All patients had gastric lavage and charcoal, the timing and dosing of which were performed at the treating physician’s discretion Eight healthy volunteers given 50 mg doxepin followed by 15 g activated charcoal after 30 min</td>
<td>Correlation between estimated plasma amitriptyline concentration half-life and time to charcoal</td>
<td>Directly proportional (r=0.78, p&lt;0.05)</td>
<td>Small numbers. No data on time to gastric lavage. Five patients received a second dose of charcoal which may have affected the results. Dose of charcoal not standardised</td>
</tr>
<tr>
<td>Scheinin et al, 1985, Finland</td>
<td>Experimental, volunteer study</td>
<td>Healthy volunteers given 75 mg nortriptyline. Control session: no intervention. Treatment session: 10 g Medicol at 30 min. Plasma nortriptyline levels measured after 2, 4, 6, 10, 24, 32 and 48 h</td>
<td>Experimental, crossover design</td>
<td>No significant differences (p=0.25)</td>
<td>Small dose of TCA and charcoal. Study in fasted volunteers. The results cannot be directly extrapolated to the population with TCA overdose</td>
</tr>
</tbody>
</table>
### Table AII Continued

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crome et al, 1983, UK77</td>
<td>48 patients with suspected TCA overdose. All had gastric lavage. 10 g Medicinal versus nothing</td>
<td>PRCT</td>
<td>Plasma TCA concentration</td>
<td>No difference in rate of fall noted</td>
<td>Small numbers with complications. Small charcoal dose. 18 patients excluded. Time from ingestion to charcoal not investigated. No data on numbers also given gastric lavage</td>
</tr>
<tr>
<td>Hulten et al, 1988, multinational35</td>
<td>77 patients &gt;14 years with TCA overdose. Randomised to receive either gastric lavage alone (control, n=43) or gastric lavage and activated charcoal 20 g (n=34)</td>
<td>PRCT</td>
<td>Plasma TCA concentration</td>
<td>No significant difference in peak or half-life</td>
<td>Control group differed from charcoal group at baseline. No data regarding the timing of charcoal administration</td>
</tr>
<tr>
<td>Karkkainen and Neuvonen, 198678</td>
<td>Six healthy volunteers. Each took 75 mg amitriptyline. 50 g charcoal within 5 min</td>
<td>Experimental</td>
<td>Plasma TCA bioavailability (area under the concentration-time curve)</td>
<td>Decreased by 99% compared with controls</td>
<td></td>
</tr>
</tbody>
</table>

### Table AIII Multiple dose activated charcoal following tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crome, 1977, UK76</td>
<td>12 healthy volunteers administered 75 mg nortriptyline; 5 received single dose activated charcoal (5 g), 7 received single dose activated charcoal plus multidose regimen (4×5 g) the following week. All participants were in control group which received nothing</td>
<td>PRCT</td>
<td>% Reduction in peak plasma levels</td>
<td>Multidose &gt; single dose (72% reduction vs 58%), p&lt;0.05</td>
<td>Volunteers used, hence results may not be valid since patient did not take overdose levels. Activated charcoal administered 30 min following nortriptyline; however, in clinical setting, most patients do not present within 30 min. Not randomised, not blinded, small number.</td>
</tr>
<tr>
<td>Schwartz et al, 1984, USA79</td>
<td>Eight healthy volunteers given 50 mg doxepin. Control group received nothing vs single dose 15 g activated charcoal and repeated dose 15 g activated charcoal at 3 h and 10 g after 6, 9, 12 and 24 h</td>
<td>Non-randomised controlled trial</td>
<td>% Reduction nortriptyline availability</td>
<td>Multidose &gt; single dose (70% reduction vs 55%), p&lt;0.05</td>
<td>Volunteers used, hence results may not be valid since patient did not take overdose levels. Activated charcoal administered 30 min following nortriptyline; however, in clinical setting, most patients do not present within 30 min. Not randomised, not blinded, small number.</td>
</tr>
<tr>
<td>Scheinin et al, 1985, Finland75</td>
<td>Eight healthy volunteers given 50 mg doxepin. Control group received nothing vs single dose 15 g activated charcoal and repeated dose 15 g activated charcoal at 3 h and 10 g after 6, 9, 12 and 24 h</td>
<td>Non-randomised controlled trial</td>
<td>Total plasma clearance (doxepin)</td>
<td>Reduced half-life below 10 h for each patient to as low as 4 h</td>
<td>Volunteers used, hence results may not be valid since patient did not take overdose levels. Activated charcoal administered 30 min following nortriptyline; however, in clinical setting, most patients do not present within 30 min. Not randomised, not blinded, small number.</td>
</tr>
<tr>
<td>Karkkainen et al, 198678</td>
<td>Amitriptyline 75 mg administered orally to six fasted volunteers. Activated charcoal 50 g given 6 h after amitriptyline dose and further doses (12.5 g) of charcoal at 12, 18, 24, 30, 36, 42, 48 and 54 h</td>
<td>PRCT</td>
<td>Half-life</td>
<td>Reduced half-life by 20% from 27.4±(SE) 4.8 h (control) to 21.1±3.3 h (charcoal group)</td>
<td>Small group. Lack of description in Methods. Single group received charcoal at 30 min, which explains its low peak concentration in comparison with other groups; however, this is not mentioned as a potential confounding variable. Comparison of variables between groups is difficult due to the weakness mentioned above. Investigators not blinded, no randomisation. Did not receive overdose amounts of doxepin, hence implications of validity.</td>
</tr>
<tr>
<td>Ilett et al, 199110</td>
<td>Three patients with dothiepin overdose treated with repeated activated charcoal</td>
<td>Observational study</td>
<td>Mean half-life</td>
<td>12.1±1.3 h compared to literature range of 18.5–24 h.</td>
<td>Small number. No control group</td>
</tr>
</tbody>
</table>
### Table AIV Gastric lavage following tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulten et al, 1988, Sweden 28</td>
<td>91 patients with suspected TCA overdose. 43 gastric lavage only, 34 gastric lavage + 20 g activated charcoal</td>
<td>PRCT</td>
<td>Peak plasma concentrations</td>
<td>No difference</td>
<td>Only 20 g of charcoal used. All patients received gastric lavage as standard (no comparison of charcoal vs lavage)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma half-lives</td>
<td>No difference</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma drug concentration versus time curve</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Toxic symptoms</td>
<td>Toxic symptoms greater in gastric lavage only group but this was not statistically significant</td>
<td></td>
</tr>
<tr>
<td>Bosse et al, 1995, USA 34</td>
<td>51 TCA overdose. Group 1: 50 g charcoal only (n=22); group 2: lavage followed by 50 g charcoal (n=14); group 3: 25 g charcoal followed by lavage then 25 g charcoal (n=15)</td>
<td>PRCT</td>
<td>Mean length of stay in hospital (h)</td>
<td>No significant difference (1) 93.3; (2) 107.2; (3) 66.7 (p=0.473)</td>
<td>Not blinded. Small numbers. Variations between presenting GCS and drug levels between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean length of stay in ICU (h)</td>
<td>No significant difference (1) 66.9; (2) 54.1; (3) 34.4 (p=0.436)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mean duration sinus tachycardia (h)</td>
<td>No significant difference (1) 20.8; (2) 30.8; (3) 32.2 (p=0.594)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean mechanical ventilation time (h)</td>
<td>No significant difference (1) 43.4; (2) 24.1; (3) 17.8 (p=0.321)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspiration</td>
<td>No significant difference (1) 2/22; (2) 3/14; (3) 15/3 (p=0.501)</td>
<td></td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Score.

### Table AV ECG and serum drug levels for predicting complications

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al, 2004 41</td>
<td>Papers identified from Medline and Cochrane register for studies that investigated criteria for predicting outcomes in TCA overdose. Papers assessed by two investigators. Studies included if possible to construct 2×2 table from TCA concentration or ECG abnormalities against clinical outcomes. The following diagnostic tests were evaluated: (1) TCA concentration; (2) QRS &gt;0.19 s; (3) QTc &gt;430 ms; (4) R/S ratio &gt;0.7; (5) right axis deviation of 120–270° in terminal 40 ms frontal plane QRS vector (T40)</td>
<td>Systematic review and meta-analysis</td>
<td>Number of studies</td>
<td>941 studies found, 18 studies included in the review</td>
<td>All but one studies retrospective, most non-blinded, time between ingestion and measurement not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled sensitivity and specificity to predict death</td>
<td>QRS=0.91 and 0.62; TCA concentration = 0.76 and 0.60; QTc= 0.50 and 0.68; T40=0.33 and 0.71, respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled sensitivity and specificity to predict seizures</td>
<td>QRS=0.69 and 0.69; TCA concentration = 0.75 and 0.72; T40=0.50 and 0.72, respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled sensitivity and specificity to predict ventricular arrhythmias</td>
<td>QRS=0.79 and 0.46; TCA concentration=0.78 and 0.57; QTc=0.78 and 0.56;T40=0.33 and 0.71; R/S ratio=0.47 and 0.97, respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive and negative likelihood ratios for death</td>
<td>QRS=2.13 and 0.31; TCA concentration=1.90 and 0.57; QTc=1.56 and 0.74; T40=1.14 and 0.94, respectively</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Positive and negative likelihood ratios for seizures</td>
<td>QRS=3.18 and 0.38; TCA concentration = 2.39 and 0.46; T40 = 1.79 and 0.69, respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive and negative likelihood ratios for ventricular arrhythmias</td>
<td>QRS=1.46 and 0.46; TCA concentration = 1.81 and 0.39; QTc=1.77 and 0.39; T40=1.14 and 0.94; R/S ratio=15.7 and 0.55, respectively</td>
<td></td>
</tr>
</tbody>
</table>

TCA, tricyclic antidepressant.

### Table AVI Venous versus arterial blood gas sampling

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eizadi-Moqaddam et al, 2005, Iran 42</td>
<td>50 patients with clinical manifestations of TCA poisoning who presented to the ED. Samples for arterial and venous gas analysis obtained at presentation and 30 min after bolus sodium bicarbonate therapy</td>
<td>Prospective diagnostic cohort study</td>
<td>Mean (SD) pH on admission</td>
<td>Venous 7.34 (0.0049); arterial 7.37 (0.0052) (p=0.00)</td>
<td>Small statistically significant differences in parameters identified but clinical significance of the difference in parameters not assessed. No attempt to correlate blood gas parameters with incidence of complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) HCO₃⁻ 30 min after bicarbonate</td>
<td>Venous 25.24 (3.35); arterial 23.78 (3.11) (p=0.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) pH 30 min after bicarbonate</td>
<td>Venous 7.34 (0.049); arterial 7.37 (0.042) (p=0.012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) PCO₂ on admission</td>
<td>Venous 43.79 (6.39); arterial 38.47 (7.10) (p=0.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) PO₂ on admission</td>
<td>Venous 42.50 (10.78); arterial 79.94 (15.94) (p=0.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) HCO₃⁻ 30 min after bicarbonate</td>
<td>Venous 23.26 (3.23); arterial 22.19 (3.28) (p=0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linear regression model (arterial and venous pH measurements)</td>
<td>Significant relationship (p&lt;0.001). r²=0.60</td>
<td></td>
</tr>
</tbody>
</table>

ED, emergency department; PCO₂, PO₂, carbon dioxide and oxygen tensions; TCA, tricyclic antidepressant.


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### Table AVII  Sodium bicarbonate following tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al, 1973, Australia</td>
<td>4 children aged 18 months to 3 years</td>
<td>Case series</td>
<td>Blood pressure</td>
<td>Normalised</td>
<td>Case series only. Causal relationship between sodium bicarbonate and clinical improvement not established</td>
</tr>
<tr>
<td>Brown, 1976, Australia</td>
<td>12 children aged 15 months to 12 years with arrhythmias. Sodium bicarbonate 0.5-2 mEq/kg</td>
<td>Case series</td>
<td>Reversion of dysrhythmias to sinus rhythm</td>
<td>9/12 reverted to sinus rhythm</td>
<td>Case series only. Causal relationship between sodium bicarbonate and clinical improvement not established</td>
</tr>
<tr>
<td>Koppel et al, 1992, Germany</td>
<td>184 cases of overdose. 8 patients with cardiac disturbance. 100 mmol sodium bicarbonate administered</td>
<td>Retrospective cohort study</td>
<td>Rhythm</td>
<td>4/8 reverted to sinus rhythm</td>
<td>Small numbers. No comparison with control group. In some cases, mixed overdose with chlordiazepoxide</td>
</tr>
<tr>
<td>Hoffmann et al, 1993, USA</td>
<td>91 patients with overdose. Sodium bicarbonate to pH of 7.55</td>
<td>Retrospective cohort study</td>
<td>Blood pressure (SBP)</td>
<td>20/21 normalised (&gt;90 mm Hg systolic)</td>
<td>No adequate control group. Physicians not blinded. Data may be missing from notes since retrospective study</td>
</tr>
</tbody>
</table>

### Table AVIII  Intravenous catecholamines to treat hypotension following tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teba et al., 1988, USA</td>
<td>Case 1: 47-year-old woman, BP 66 mm Hg. Case 2: 56-year-old woman, BP 52 mm Hg. Both treated with sodium bicarbonate and dopamine without significant improvement in hypotension in 15 dogs infused with amitriptyline HCl.</td>
<td>Case report</td>
<td>Systemic systolic BP (SBP)</td>
<td>Case 1: Continuous infusion of norepinephrine increased SBP from 68 mm Hg to &gt;100 mm Hg. Case 2: Following norepinephrine infusion SBP increased from 52 mm Hg to 130 mm Hg</td>
<td>Only 2 case reports. These may be exceptional cases</td>
</tr>
<tr>
<td>Vernon et al, 1991, USA</td>
<td>Received dopamine 5, 15 and 30 µg sequentially or norepinephrine 0.25, 0.5 and 1.0 µg sequentially. Haemodynamic measurements after each dose</td>
<td>Experimental randomised controlled trial</td>
<td>Mean arterial pressure (MAP) (mm Hg)</td>
<td>All doses of norepinephrine &gt; MAP compared with control (p&lt;0.05). Two higher dopamine doses &gt; MAP compared with control (p&lt;0.05). At highest dose, no significant difference between norepinephrine and dopamine</td>
<td>Animal study. Not blinded. Randomisation questionable. Small number. Each catecholamine infusion given sequentially</td>
</tr>
<tr>
<td>Cardiac output (CO) (l/min)</td>
<td>All doses of norepinephrine &gt; CO than control (p&lt;0.05). Two higher dopamine doses &gt; CO than control (p&lt;0.05). At highest dose, no significant difference between norepinephrine and dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak left ventricular (LV) dP/dt (rate of change of LV pressure)</td>
<td>All doses of norepinephrine &gt; LV dP/dt than control (p&lt;0.05). Two higher dopamine doses &gt; LV dP/dt than control (p&lt;0.05). At highest dose, no significant difference between norepinephrine and dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (SVO2)</td>
<td>All doses of norepinephrine &gt; SVO2 than control (p&lt;0.05). Two higher dopamine doses &gt; LV SVO2 than control (p&lt;0.05). At highest dose, no significant difference between norepinephrine and dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance (SVR)</td>
<td>All doses of norepinephrine &gt; SVR than control (p&lt;0.05). At highest dose, no significant difference between norepinephrine and dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knudsen and Abrahamsson, 1994, Sweden</td>
<td>86 male Wistar rats infused with amitriptyline HCl. Treated with: epinephrine; norepinephrine; epinephrine + magnesium; norepinephrine + magnesium; Milrinone</td>
<td>Non-randomised controlled intervention trial</td>
<td>Survival</td>
<td>Epinephrine + norepinephrine &gt; survival than control (p&lt;0.001). Epinephrine &gt; norepinephrine survival rate</td>
<td>Animal study: can it be useful in humans? Not blinded. Small number. Raw data absent in some measurements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase in QRS duration</td>
<td>Epinephrine significantly lower increase in QRS compared with control + norepinephrine groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Onset arrhythmia</td>
<td>Epinephrine delayed onset of arrhythmias compared with control (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration sinus rhythm</td>
<td>Epinephrine &gt; control (p&lt;0.01) Epinephrine &gt; norepinephrine (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QRS duration</td>
<td>Epinephrine treatment groups &gt; survival rates than norepinephrine treatment groups (p&lt;0.01). Treatment groups &gt; survival rate than control groups (p&lt;0.01). Epinephrine + sodium bicarbonate treatment &gt; survival rate than epinephrine alone (p&lt;0.01). Norepinephrine + sodium bicarbonate treatment &gt; survival rate than norepinephrine alone (p&lt;0.01)</td>
<td>Animal study hence extrapolation to humans may be difficult. Not blinded. Raw data unavailable in some measurements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arrhythmias</td>
<td>Epinephrine-treated rats had a longer time to onset of arrhythmias than norepinephrine-treated rats (21.5 vs 11.6 min) (p&lt;0.05). Epinephrine + sodium bicarbonate-treated rats had the longest time in sinus rhythm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QRS duration</td>
<td>Epinephrine treatment associated with shorter QRS interval than norepinephrine treatment (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Knudsen and Abrahamsson, 1997, Sweden</td>
<td>91 male Sprague-Dawley rats. All given amitriptyline HCl infusion at 2 mg/kg/min for 60 min. After 5 min given either: (a) epinephrine infusion + 5 min bolus sodium bicarbonate; (b) norepinephrine infusion + 5 min bolus sodium bicarbonate; (c) epinephrine infusion + 5 min bolus placebo; (d) norepinephrine infusion + 5 min bolus placebo; (e) placebo infusion + 5 min bolus sodium bicarbonate; (f) placebo infusion + 5 min bolus placebo (placebo infusion= glucose 5%; placebo bolus = sodium chloride (9 mg/ml) 1 ml/kg/min</td>
<td>Non-randomised, animal controlled intervention trial</td>
<td>Survival</td>
<td>Epinephrine + sodium bicarbonate &gt; survival rate than other groups (p&lt;0.01). Epinephrine treatment groups &gt; survival rates than norepinephrine treatment groups (p&lt;0.01). Treatment groups &gt; survival rate than control groups (p&lt;0.01). Epinephrine + sodium bicarbonate treatment &gt; survival rate than epinephrine alone (p&lt;0.01). Norepinephrine + sodium bicarbonate treatment &gt; survival rate than norepinephrine alone (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arterial blood pressure (MAP)</td>
<td>All doses of norepinephrine and two higher doses of epinephrine increased MAP. Norepinephrine &gt; epinephrine at low and intermediate doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality at 75 min (%)</td>
<td>Control group=75%; norepinephrine=45%; epinephrine=27%. At intermediate dose, epinephrine group had lowest death risk (p=0.012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arrhythmias</td>
<td>Intermediate dose: norepinephrine &gt; arrhythmia than epinephrine (p&lt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>
Table AXI  Glucagon to treat haemodynamic instability after tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruddy et al, 1972, Australia</td>
<td>4-year-old ingested approx 1000 mg imipramine, episode of PEA 1.5 h duration</td>
<td>Case report</td>
<td>Cardiac status</td>
<td>Improved with 1 mg boluses glucagon</td>
<td>Case report. Patient also received pyridostigmine, sodium bicarbonate, isoprenaline, digoxin, lidocaine and mannitol.</td>
</tr>
<tr>
<td>Senes et al, 1995, UK</td>
<td>25-year-old woman. Plasma toxicology: imipramine 3.0 mg/l, desipramine 0.18 mg/l, diazepam 2.9 mg/l, nortrazepam 2.2 mg/l, chlorpromazine 0.3 mg/l, temazepam 0.25 mg/l</td>
<td>Case report</td>
<td>Blood pressure</td>
<td>No response to 1 mg bolus glucagon. 40 mm Hg systolic rise after glucagon</td>
<td>Multiple drugs ingested in overdose. Patient also received sodium bicarbonate, phentoin and isoprenaline and fluid resuscitation.</td>
</tr>
<tr>
<td>Sensky et al, 1999, UK</td>
<td>36-year-old OD admission. Toxicology dothiepin 2.58 mg/l, desmethyldothiepin 0.51 mg/l, paracetamol 135 mg/l, diazepam 0.33 mg/l, nortrazepam 0.12 mg/l</td>
<td>Case report</td>
<td>Blood pressure</td>
<td>No response to 1 mg bolus glucagon. 30 mm Hg systolic rise after glucagon</td>
<td>Case report. Multiple drugs ingested in overdose. Patient also received N-acetylcysteine, epinephrine, norepinephrine, ephedrine, dobutamine and aminophylline with fluid restriction.</td>
</tr>
</tbody>
</table>

Table AX  Magnesium sulphate to treat dysrhythmias following TCA overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knudsen and Abrahamsson, 1997, Sweden</td>
<td>44-year-old woman admitted after an overdose of amitriptyline. She suffered a cardiac arrest (ventricular fibrillation) after 12 h</td>
<td>Case study</td>
<td>Observed effect of cardiopulmonary resuscitation, sodium bicarbonate, defibrillation (four attempts), lidocaine and epinephrine (&quot;several doses&quot;)</td>
<td>Patient remained in ventricular fibrillation</td>
<td>Only a case study. Observed effects may or may not have been partly due to the effect of magnesium sulphate</td>
</tr>
<tr>
<td>Citak et al, 2002, Turkey</td>
<td>23-month-old boy who had taken 36 mg/kg amitriptyline and had been successfully resuscitated from cardiac arrest after 70 min. Following return of circulation, he was in ventricular tachycardia (VT)</td>
<td>Case study</td>
<td>Observed effect of lidocaine, bicarbonate and attempted electrical cardioversion</td>
<td>Spontaneous return of circulation; &quot;stable regular heart rhythm&quot;. Haemodynamic performance normalised</td>
<td>Case study. Observed effects may or may not have been partly due to the effects of magnesium sulphate</td>
</tr>
<tr>
<td>Sarisoy et al, 2007, Turkey</td>
<td>4-year-old boy who had taken 70 mg/kg amitriptyline Glasgow Coma Score 3/15, bradycardia and hypertension on arrival. Cardiac arrest (VF) despite epinephrine, bicarbonate, lidocaine and normal saline. VT after &quot;synchronised cardioversion&quot; of VF. Then loaded with 2 g magnesium sulphate followed by infusion of 3 mg/min</td>
<td>Case report</td>
<td>Reversion of VT</td>
<td>After magnesium infusion, &quot;normal cardiac rhythm&quot; was obtained</td>
<td>Case report. Magnesium infusion may not have caused termination of VT (multiple other therapies given; may have resolved spontaneously). Some unusual features regarding the management of this patient</td>
</tr>
</tbody>
</table>

Table AXI  Lipid emulsion for treatment of TCA toxicity

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minton et al, 1987, UK</td>
<td>Four healthy volunteers aged 21–27 years who were given amitriptyline 75 mg once daily for 10 days. On the 8th and 10th days they were cannulated and randomly assigned to receive either saline infusion or lipid emulsion (500 ml Intralipid 20% given over 5 h), with crossover design. Blood was taken prior to infusion, at 2 h and 5 h for levels of amitriptyline, its metabolite (nortriptyline) and lipids</td>
<td>Prospective crossover randomised controlled volunteer study</td>
<td>Mean levels of amitriptyline + nortriptyline</td>
<td>13.8% higher at the end of lipid treatment compared with saline group (p &lt; 0.05)</td>
<td>Small numbers. Therapeutic doses of amitriptyline given over 8 days; may perform differently in an acute overdose situation with ongoing gastric absorption and signs of toxicity.</td>
</tr>
</tbody>
</table>

(OD, overdose; PEA, pulseless electrical activity.)
### Table AXII Observations of asymptomatic patients following tricyclic antidepressant (TCA) overdose

<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenland and Howe, 1981, USA</td>
<td>62 patients with TCA overdose</td>
<td>Retrospective cohort study</td>
<td>Cardiac arrhythmias</td>
<td>No cardiac arrhythmias occurred after the first 24 h in any patient free of such complication earlier</td>
<td>Lack of raw data; important details may be missing in retrospective study</td>
</tr>
<tr>
<td>Pentel and Sioris, 1981, USA</td>
<td>Patients with TCA overdose. All underwent gastric emptying</td>
<td>Retrospective cohort study</td>
<td>Development of complications</td>
<td>All patients who developed complications did so within 1 h of hospitalisation. No patients developed arrhythmias after being alert and having a normal ECG for 1 h.</td>
<td>Does not mention the exact number of patients in the study. VITAL data may be missing from notes due to retrospective study</td>
</tr>
<tr>
<td>Goldberg et al, 1985, USA</td>
<td>75 patients with TCA overdose</td>
<td>Retrospective cohort study</td>
<td>Cardiac complications</td>
<td>No new complications after 24 h</td>
<td>Data may be missing due to retrospective study. No actual data on times of complications following overdose.</td>
</tr>
<tr>
<td>Enerman et al, 1987, USA</td>
<td>92 patients with TCA overdose admission from 1975 to 1985</td>
<td>Retrospective cohort study</td>
<td>Development of complications (26/37 patients had documentation)</td>
<td>19/26 developed complications within 30 min. 17/26 developed complications between 30 and 120 min</td>
<td>Data may be missing due to retrospective study</td>
</tr>
<tr>
<td>Tokarski and Young, 1988, USA</td>
<td>Review of 45 patients with TCA overdose from 1992 to 1985 and algorithm applied</td>
<td>Retrospective cohort study</td>
<td>Patient discharged using algorithm (no major signs of toxicity/QRS &lt; 0.10 in 6 h)</td>
<td>20 patients would have been discharged since no signs of major toxicity or QRS was &lt; 0.10 s within 6 h of admission. None of these patients developed any complications</td>
<td>Small sample. Retrospective study, hence vital data from notes may be missing</td>
</tr>
<tr>
<td>Banahan and Schelkun, 1990, USA</td>
<td>Review of 33 patients with an admission diagnosis of TCA overdose between January 1985 and December 1988. Tokarski and Young algorithm applied (see above)</td>
<td>Retrospective cohort study</td>
<td>Patients discharged under algorithm by Tokarski and Young (see above)</td>
<td>11 patients did not show signs of major toxicity or QRS &gt; 0.10 s within 6 h. Using the algorithm, these patients could have been discharged. None developed any complications</td>
<td>Small sample. Retrospective study, hence data may be missing</td>
</tr>
<tr>
<td>Hulten et al, 1992, Sweden</td>
<td>67 patients with TCA overdose</td>
<td>Cohort study</td>
<td>Development of complications</td>
<td>All patients who developed complications did so within 6 h of admission</td>
<td>Lack of raw data. No sample size estimation performed</td>
</tr>
</tbody>
</table>

### APPENDIX 2: SEARCH FILTERS

#### TCA filter

(exp Antidepressive Agents, Tricyclic/OR tricyclic.mp. OR amitriptyline.mp. OR exp Amloptryptiline/OR desipramine.mp. OR exp Desipramine/OR clomipramine.mp. OR exp Clomipramine/OR doxepin.mp. OR exp Doxepin/OR dothepin.mp. OR exp Dothepin/OR imipramine.mp. OR exp Imipramine/OR lofepramine.mp. OR exp Lofepramine/OR nortriptyline.mp. OR exp Nortriptyline/OR trimipramine.mp. OR exp Trimipramine/)

#### Charcoal filter

(exp Charcoal/OR charcoal.mp.)

#### Lavage filter

(gastric lavage.mp. OR exp Gastric Lavage/OR irrigation.mp. OR exp Irrigation/OR lavage.mp. OR exp Decontamination/OR gastric decontamination.mp. OR washout.mp. OR gut decontamination.mp OR exp Stomach Emptying/OR exp Stomach Lavage/)

#### Overdose filter

(exp Overdose/OR exp Poisoning/OR overdose.mp. OR exp Drug Overdose/)

#### ECG Filter

(ECG.mp. OR exp Electrocardiography/ OR electrocardiogram.mp. OR EKG.mp.)

#### Vasopressor filter

(exp Catecholamines/OR exp Epinephrine/OR exp Norepinephrine/OR exp Dopamine/OR catecholamine OR epinephrine OR norepinephrine OR dopamine OR epinephrine OR norepinephrine.mp.)

#### Bicarbonate filter

(exp Sodium Bicarbonate/OR exp Bicarbonates/OR (sodium bicarbonate OR bicarbonates).mp.)

#### Observation filter

(exp Monitoring, Physiologic/OR exp Patient Admission/OR (admission OR monitoring).mp.)

#### Benzodiazepine filter

(exp Benzodiazepines/OR exp Diazepam/OR exp Clonazepam/OR exp Midazolam/OR exp Temazepam/OR exp Nirtazepam/OR (benzodiazepine OR diazepam OR clonazepam OR nirtazepam OR midazolam OR temazepam).mp.)

#### Phenothiazine filter

(exp Phenytoin OR phenytin.mp. OR epilim.mp.)

#### Seizure filter

(exp Seizure/OR (seizur$ OR convuls$ OR fitting OR fit OR fits).mp.)

#### Intubation filter

(exp Intubation, Intratracheal/OR (rapid sequence induction).mp OR rsi.mp OR intubation.mp OR (crash induction).mp OR airway management.mp).

#### Sedation filter

(exp Hypnotics and Sedatives/OR sedation.mp. OR sedat$.mp. OR hypnotic$.mp.)

#### pH filter

(exp Hydrogen Ion Concentration/OR pH.mp.)

#### Blood gas filter

(Exp Blood Gas Analysis/OR exp Blood Gas/ OR blood gas$.mp.)

#### Unconsciousness filter

(Glasgow Coma Scale.mp. OR exp Coma/OR exp Glasgow Coma Scale/OR exp Unconsciousness/OR (unconscious$ OR semiconscious$ OR obtund$ OR unresponsive$).mp.)

#### Hypotension filter

(exp Hypotension/OR (hypotension OR hypotensive).mp.)
**GEMNet guidelines**

**Intravenous fluids filter**
(exp Infusion/OR exp Infusion Fluid/ OR exp Colloid/ OR exp Polygeline/OR exp Gelatin Succinate/ OR exp Sodium Chloride/OR (infusion OR colloid OR gelofusine OR haemaccel OR saline).mp.)

**Magnesium filter**
(exp Magnesium/OR exp Magnesium Sulfate/OR magnesium.mp.)

**Dysrhythmias filter**
(exp Heart Ventricle Tachycardia/ OR exp Heart Arrhythmia/ OR exp Arrhythmias, Cardiac/ OR (dysrhythmias$ OR arrhythmia$).mp.)

**Glucagon filter**
(exp Glucagon/OR glucagon.mp.)

**Lipid emulsion filter**
(intralipid.mp. OR exp Fat Emulsions/OR exp Fat Emulsions, Intravenous/)
Guidelines in Emergency Medicine Network (GEMNet): guideline for the management of tricyclic antidepressant overdose

Richard Body, Tom Bartram, Fawad Azam and Kevin Mackway-Jones

doi: 10.1136/emj.2010.091553

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