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

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

Emergency Department, Manchester Royal Infirmary, Manchester, UK

Correspondence to
Richard Body, Emergency Department, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK; rbody@doctors.org.uk

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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.[1]

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.[2] Despite this, TCA overdose still accounts for up to 18% of all poisoning deaths in the UK.[3] 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.[4] In the UK in 2005 there were 272 deaths related to TCA overdose.[5]

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.[6–11] The anticholinergic effects of TCAs may also lead to dry mouth, blurred vision, dilated pupils, hyperthermia and delayed gastric emptying.[12 13] Intestinal obstruction and perforation have been reported,[14 15] as has pancreatitis.[16] Finally, TCAs exert a number of effects on the central nervous system which may lead to drowsiness, coma, respiratory depression, seizures and delirium.[17–20] Opthalmoplegia has also been reported.[21 22] Many patients require intensive care support or hospital admission.[19 20]

To date, the Toxbase database provided by the National Poisons Information Service has been the initial portal for treatment advice in TCA overdose.[23] 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.[24]

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 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.[25] 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.[26] 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.[27] 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, hypoventilation 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 (>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

- 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)**.

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 AI).

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, hypoventilation and aspiration pneumonia following drug overdose.

Of interest, both Hulten *et al*[28] and Emerman *et al*[29] 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 al*[30] 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 hypoventilation 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, hypoventilation 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

a. Activated charcoal.
b. Multiple dose activated charcoal.
c. 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.[32] 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. Eight papers were relevant to the three-part question (table AII).

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 was directly correlated with estimated plasma TCA half-life.[33] However, the study involved small numbers and had significant weaknesses, meaning that it is difficult to interpret the results. Three randomised controlled trials of charcoal have been reported.[33–35] None of these trials was able to demonstrate a significant improvement in clinical outcome following charcoal administration. Furthermore, in one study of 51 patients, 15.7% of patients aspirated.[34]

As pulmonary aspiration is a significant risk in patients with TCA overdose and a well-described complication of activated charcoal administration, caution should be exercised before prescribing activated charcoal in this patient group.[36–41]

Clinical bottom line

There is no clinical evidence that activated charcoal is of benefit in patients with TCA overdose. Experimental data suggest that drug absorption may be reduced. Activated charcoal may be considered within 1 h of significant drug overdose, but the potential for pulmonary aspiration should be strongly considered before use.

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. One study was excluded due to insufficient quality (table AIII).

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*[42] 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 13 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-eighty studies were found 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* shows that QRS duration and serum drug levels are roughly equivalent for predicting complications including death, seizures and ventricular arrhythmias. The use of the ECG allows rapid and repeated measurement in the emergency setting. It may be immediately examined for multiple abnormalities, each of which may aid in the prediction of complications. While the serum drug level provides comparable predictive value, it has the disadvantages of being more invasive, taking longer to obtain results and being less widely available in the ED.

Future research may concentrate on multivariate analysis to determine which variables are independent predictors of complications, ideally with a view to deriving a clinical decision rule to guide management and disposition of patients who have taken a TCA overdose.

Clinical bottom line

The ECG is preferable to serum drug level for the prediction of complications following TCA overdose.

Recommendations

- 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)**.

ECG changes as predictors of severity of overdose

Three-part question

In (TCA overdose) which (ECG abnormalities) are (predictive of death, 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-eighty 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).

Comments

The ECG has long been used to aid in the risk stratification and management of patients who have taken a TCA overdose. 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 >430 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-eighty 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.

Clinical bottom line

Local advice should be followed.

Arterial or venous blood gas estimation for monitoring and risk stratification following TCA overdose

Three-part question

In (patients who have taken an overdose of TCAs) does (measurement of arterial or venous blood gases) lead to (superior risk stratification and monitoring of blood pH)?

Search strategy

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

Search outcome

A total of 81 papers were identified (65 in Medline, 18 in Embase). One paper was directly relevant to the three-part question (table AVI).

Comments

Assessment of acid-base balance is an essential part of the initial assessment and monitoring of patients who have taken a significant overdose of TCAs. An important part of the management of these patients is alkalinisation, which has been reported to result in profound alkalaemia and high mortality.[46] However, arterial blood sampling is often painful. In alert patients who do not have suspected hypoventilation, venous blood gas analysis would be preferable if it could be shown to be equivalent for risk stratification and monitoring.

The only relevant paper did seek to answer this question directly and had an appropriate sample size. Although statistically significant differences were detected in all relevant parameters between arterial and venous blood gas analysis, the clinical effects of the differences in bicarbonate and pH (in particular) are questionable. Furthermore, a fairly strong linear relationship was demonstrated between arterial and venous pH measurements.

The study did not attempt to determine which sampling method enabled superior prediction of complications. However, the evidence is sufficient to recommend that venous blood gas analysis is likely to be acceptable for the initial assessment and subsequent monitoring of these patients so long as hypoxia or hypoventilation are not suspected.

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

a. Intravenous fluids
b. Sodium bicarbonate
c. Vasopressors
d. Glucagon
e. Magnesium sulphate
f. 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,[47] 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.[48] 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.[48] 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.[49]

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.[50] 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.[51] 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.[46]

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, 31% 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.[52]

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 (Overdose 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 temporally 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

There is not enough evidence currently available to support the routine use of glucagon in TCA overdose. It is not unreasonable to administer 10 mg intravenous glucagon to treat life-threatening hypotension or arrhythmias refractory to other measures.

Recommendation

- 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

Three-part question

In (patients who have taken an overdose of TCAs and develop dysrhythmias) does (magnesium sulphate or standard treatment) lead to (improved rates of cardioversion to sinus rhythm and haemodynamic stability)?

Search strategy

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

(TCA filter) AND (Magnesium filter) AND (Dysrhythmias filter) limit to humans and English language.

Search outcome

One hundred and eleven papers were identified (102 in Embase and 9 in Medline). No relevant comparative trials were identified. Three case studies were identified and have been tabulated (table AX). An experimental animal study was identified and is discussed.

Comment(s)

There are three reports of the successful use of magnesium sulphate for dysrhythmias associated with TCA use, two of which are from Turkey and have striking similarities. The effects have not been scientifically validated.

Knudsen and Abrahamsson[53] reported that magnesium sulphate was superior to lidocaine for the successful cardioversion of amitriptyline-induced ventricular tachycardia in rats. There are no reports of potential adverse effects of magnesium sulphate in this context.

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

may reduce toxicity by creating an intravascular lipid compartment into which lipid-soluble drugs may be sequestered.[54 55] Alternatively, lipid emulsion may work by enhancing free fatty acid metabolism.[56] 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.[57] The same group has also shown that lipid emulsion is superior to sodium bicarbonate for treatment of TCA-induced hypotension in rabbits.[58] 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 QRS prolongation in an intubated patient following TCA overdose.[59] 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

a. Phenytoin
b. Benzodiazepines

Phenytoin

Three-part question

In (patients with TCA overdose who develop prolonged seizures) does (phenytoin or benzodiazepines) lead to (quicker and more reliable termination of seizures with fewer complications)?

Search strategy

Ovid MEDLINE 1966–2007 June week 1
Ovid EMBASE 1980–2007 week 24
(TCA filter) AND (Overdose filter) AND (Phenytoin filter) limit to human and English language.

Search outcome

Seven hundred and ten papers were identified (293 in Medline and 417 in Embase). None directly answered the three-part question. Several papers discussed the use of phenytoin in TCA overdose. These are discussed.

Comment(s)

Intravenous phenytoin is licensed for use in status epilepticus. Its use in the context of TCA overdose is controversial. There have been sporadic case reports of the successful use of intravenous phenytoin for the treatment of patients with severe TCA overdose who have developed cardiac conduction abnormalities.[60 61] It is proposed that this may result from its class Ia antiarrhythmic action. However, there is evidence of interaction between the two drugs, with TCAs increasing phenytoin levels.[62 63] Owing to the narrow therapeutic window of phenytoin, this interaction is of concern. Furthermore, in an animal model phenytoin was found to increase the likelihood of ventricular arrhythmias when TCAs were also infused.[64] In light of this potential interaction, guidelines from the National Poisons Information Service state that phenytoin should be avoided in patients who have taken a TCA overdose.[65]

Clinical bottom line

Phenytoin has not been compared with benzodiazepines in patients with TCA overdose. Evidence for the benefit of phenytoin in TCA overdose comes only from sporadic case studies. As there are doubts regarding the safety of phenytoin in these patients, it should be avoided.

Recommendation

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

Benzodiazepines

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 2
Ovid EMBASE 1980–2008 week 21
(TCA filter) AND (Overdose filter) AND (Benzodiazepine filter) LIMIT to English language.

Search outcome

One thousand seven hundred 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.[66]

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.[67–70] However, in all of these cases there were significant

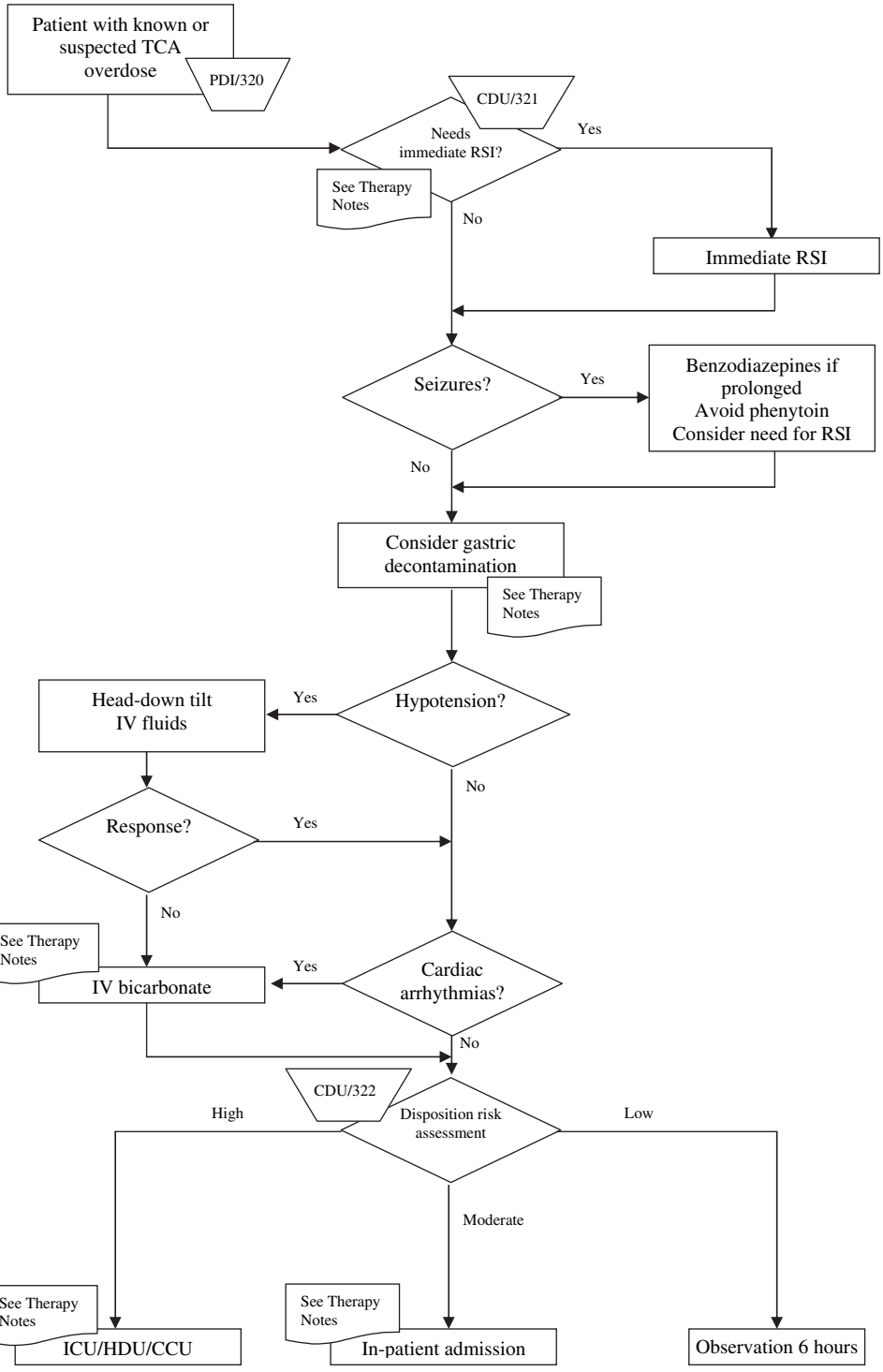

Figure 1 Evidence-based flowchart. RSI, rapid sequence induction; TCA, tricyclic antidepressant.

Figure 1 Continued.

PDI/320: SUITABILITY FOR PROTOCOL DRIVEN INVESTIGATION (ALL YES)

Over 16 years old	Yes
Known or suspected TCA overdose	Yes
No other agents ingested	Yes

Order: T, P, R, BP, SpO_2
Immediate ECG and cardiac monitor
Blood gas (venous or arterial)

CDU/321: NEED FOR IMMEDIATE RSI (ANY YES)

Airway compromise	Yes
Inadequate respiration (bradypnoea, hypoxia, significant hypercapnia)	Yes
GCS ≤8/15	Yes
Unmanageable agitation	Yes

CDU/322: DISPOSITION RISK ASSESSMENT
(HIGH IF ANY H, LOW IF ALL L AND NO H, OTHERWISE MODERATE)

Indications for RSI present	HIGH	
Persistent hypotension or inotrope/vasopressor support required	HIGH	
GCS <14/15	HIGH	
Cardiac arrhythmias	HIGH	
Alert (GCS 15/15)		LOW
Normal ECG (including QRS width <0.10s and no right axis deviation)		LOW
Normal heart rate (60-100bpm)		LOW
Systolic blood pressure ≥100mmHg		LOW
>2 hours since ingestion		LOW

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.

Clinical bottom line

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 safely be discharged.

signs of toxicity at a much earlier stage. There are no reports of late complications occurring in clinically stable patients who are alert, normotensive and have had no ECG abnormalities after 6 h of observation.

Recommendation

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

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REFERENCES

1. **National Institute for Clinical Excellence.** *Guideline development methods: information for National Collaborating Centres and guideline developers*. Updated 2005 edn. London: National Institute for Clinical Excellence, 2004.
2. **National Collaborating Centre for Mental Health.** *Depression: Management of depression in primary and secondary care*. National Institute of Clinical Excellence London, 2004. http://guidance.nice.org.uk/page.aspx?o=236667.
3. **Kerr GW,** McGuffie AC. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001;**18**:236–41.
4. **Henry JA,** Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *Br Med J* 1995;**310**:221–4.
5. **National Statistics.** The controller of HMSO. 2008. http://www.statistics.gov.uk.
6. **Kerr GW,** McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001;**18**:236–41.
7. **Brennan FJ.** Electrophysiological effects of imipramine and doxepin on normal and depressed cardiac Purkinje fibers. *Am J Cardiol* 1980;**46**:599–606.
8. **Shannon M,** Merola J, Lovejoy FH. Hypotension in severe tricyclic antidepressant overdose. *Am J Emerg Med* 1988;**6**:439–42.
9. **Thorstrand C.** Clinical features in poisonings by tricyclic antidepressants with special reference to the ECG. *Acta Med Scand* 1976;**199**:337–44.
10. **Marshall JB,** Forker AD. Cardiovascular effects of tricyclic antidepressant drugs: therapeutic usage, overdose, and management of complications. *Am Heart J* 1982;**103**:401–14.
11. **Taylor DJE,** Braithwaite RA. Cardiac effects of tricyclic antidepressant medication: a preliminary study of nortriptyline. *Br Heart J* 1978;**40**:1005–9.
12. **Hantson P,** Benaissa M, Clemessy J, *et al*. Hyperthermia complicating tricyclic antidepressant overdose. *Intensive Care Med* 1996;**22**:453–5.
13. **Kerr GW,** McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001;**18**:236–41.
14. **McMahon AJ.** Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989;**65**:948–9.
15. **Ross JP,** Small TR, Lepage PA. Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998;**64**:242–4.
16. **Roberge RJ,** Martin TG, Hodgman M, *et al*. Acute chemical pancreatitis associated with a tricyclic antidepressant (clomipramine) overdose. *J Toxicol Clin Toxicol* 1994;**32**:425–9.
17. **Callaham M,** Kassel D. Epidemiology of fatal tricyclic antidepressant poisoning: implications for management. *Ann Emerg Med* 1985;**14**:1–9.
18. **Lipper B,** Bell A, Gaynor B. Recurrent hypotension immediately after seizures in nortriptyline overdose. *Am J Emerg Med* 1994;**12**:452–3.
19. **Starkey IR,** Lawson AAH. Poisoning with tricyclic and related antidepressants—a ten year review. *Q J Med* 1980;**49**:33–49.
20. **Taboulet P,** Michard F, Muszynski J, *et al*. Cardiovascular repercussions of seizures during cyclic antidepressant poisoning. *J Toxicol Clin Toxicol* 1995;**33**:205–11.
21. **Miadinich EK,** Carlow TJ. Total gaze paresis in amitriptyline overdose. *Neurology* 1977;**27**:695.
22. **Smith MS.** Amitriptyline ophthalmoplegia. *Ann Intern Med* 1979;**91**:793.
23. **Toxbase.** 2007. http://www.spib.axl.co.uk.
24. **Mackway-Jones KM,** Carley SD, Morton RJ, *et al*. The best evidence topic report: a modified CAT for summarising the available evidence in emergency medicine. *Emerg Med J* 1998;**15**:222–6.
25. **Dunning J,** Treasure T, Versteegh M, *et al*; on behalf of the EACTS Audit and Guidelines Committee. Guideline on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. *Eur J Cardiothorac Surg* 2006;**30**:852–72.
26. **Mackway-Jones KM,** Carley SD, Morton RJ, *et al*. The best evidence topic report: a modified CAT for summarising the available evidence in emergency medicine. *Emerg Med J* 1998;**15**:222–6.
27. **Oxford Centre for Evidence Based Medicine.** 2007. http://www.cebm.net/?0=1025.
28. **Hulten BA,** Adams R, Askenasi R, *et al*. Predicting severity of tricyclic antidepressant overdose. *J Toxicol Clin Toxicol* 1992;**30**:161–70.
29. **Emerman CL,** Connors AF, Burma GM. Level of consciousness as a predictor of complications following tricyclic overdose. *Ann Emerg Med* 1987;**16**:326–30.
30. **Liisanantti J,** Kaukoranta P, Martikainen M, *et al*. Aspiration pneumonia following self-poisoning. *Resuscitation* 2003;**56**:49–53.
31. **Toxbase.** 2007. http://www.spib.axl.co.uk.
32. **Park C,** Richell-Herren K. Activated charcoal in tricyclic antidepressant overdose. *J Accid Emerg Med* 2000;**17**:126–9.
33. **Hedges JR,** Otten EJ, Schroeder TJ, *et al*. Correlation of initial amitriptyline concentration reduction with activated charcoal therapy in overdose patients. *Am J Emerg Med* 1987;**5**:48–51.
34. **Bosse GM,** Barefoot JA, Pfiefer MP, *et al*. Comparison of three methods of gut decontamination in tricyclic antidepressant overdose. *J Emerg Med* 1995;**13**:203–9.
35. **Hulten BA,** Adams R, Askenasi R. Activated charcoal in tricyclic antidepressant poisoning. *Hum Toxicol* 1988;**7**:307–10.
36. **Elliott CG,** Colby TV, Kelly TM, *et al*. Charcoal lung. Bronchiolitis obliterans after aspiration of activated charcoal. *Chest* 1989;**96**:672–4.
37. **Rajamani S,** Allen P. Accidental charcoal aspiration. *J Bronchol* 2004;**11**:130–1.
38. **Dorrington CL,** Johnson DW, Brant R. The Multiple Dose Activated Charcoal Study Group. The frequency of complications associated with the use of multiple-dose activated charcoal. *Ann Emerg Med* 2003;**41**:370–7.
39. **Givens T,** Holloway M, Wason S. Pulmonary aspiration of activated charcoal: a complication of its misuse in overdose management. *Pediatr Emerg Care* 1992;**8**:137–40.
40. **Harris CR.** Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med* 1992;**22**:1470–3.
41. **Isbister GK,** Downes F, Sibbritt D, *et al*. Aspiration pneumonitis in an overdose population: frequency, predictors and outcomes. *Crit Care Med* 2004;**32**:88–93.
42. **Kulig W,** Bar-Or D, Cantrill SV. Management of acutely poisoned patients without gastric emptying. *Ann Emerg Med* 1985;**14**:562–7.
43. **Vale JA.** Position statement: gastric lavage. *J Toxicol Clin Toxicol* 1997;**35**:711–19.
44. **Watson WA,** Leighton J, Guy J, *et al*. Recovery of cyclic antidepressants with gastric lavage [see comment]. *J Emerg Med* 1989;**7**:373–7.
45. **Boehnert MT,** Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985;**313**:474–9.
46. **Wrenn K,** Smith BA, Slovis CM. Profound alkalemia during treatment of tricyclic antidepressant overdose: a potential hazard of combined hyperventilation and intravenous bicarbonate. *Am J Emerg Med* 1992;**10**:553–5.
47. **McCabe JL,** Cobaugh DJ, Menegazzi J, *et al*. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate and hyperventilation. *Ann Emerg Med* 1998;**32**:329–33.
48. **Blackman K,** Brown SGA, Wilkes GJ. Plasma alkalinization for tricyclic antidepressant toxicity: a systematic review. *Emerg Med* 2001;**13**:204–10.
49. **Lomholt BS.** [Hyperventilation therapy in acute tricyclic antidepressant poisoning. Controlled clinical research] [In Danish]. *Ugeskr Laeger* 1975;**138**:4–9.
50. **Hoffman JR,** Votey SR, Bayer M, *et al*. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe cyclic antidepressant overdose. *Am J Emerg Med* 1993;**11**:336–41.
51. **Molloy DW,** Penner SB, Rabson J, *et al*. Use of sodium bicarbonate to treat tricyclic antidepressant induced arrhythmias in a patient with alkalosis. *Can Med Assoc J* 1984;**130**:1457–9.
52. **Seger DL,** Hantsch C, Zavoral T, *et al*. Variability of recommendations for serum alkalinization in tricyclic antidepressant overdose: a survey of US poison center medical directors. *J Toxicol Clin Toxicol* 2003;**41**:331–8.
53. **Knudsen K,** Abrahamsson J. Magnesium sulphate in the treatment of ventricular fibrillation in amitriptyline poisoning. *Eur Heart J* 1997;**18**:881–2.
54. **Weinberg G,** Vade Boncouer T, Ramaraju GA, *et al*. Pretreatment or resuscitation with a lipid emulsion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998;**88**:1071–5.
55. **Weinberg G,** Ripper R, Feinstein DL, *et al*. Lipid emulsion infusion rescues dogs from bupivacaine induced cardiac toxicity. *Reg Anesth Pain Med* 2003;**28**:198–202.
56. **Van der Velde M,** Woutens PF, Rolf N, *et al*. Long-chain triglycerides improve recovery from myocardial stunning in conscious dogs. *Cardiovasc Res* 1996;**32**:1008–15.
57. **Harvey M,** Cave G, Hoggett K. Correlation of plasma and peritoneal diasylate clomipramine concentration with haemodynamic recovery after intralipid infusion in rabbits. *Acad Emerg Med* 2009;**16**:151–6.

58. **Harvey M,** Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. *Ann Emerg Med* 2007;**49**:178—85.
59. **Brooks C.** Intralipid use in TCA overdose. 2009. http://www.intralipid.org (accessed 18 Jan 2010).
60. **Hagerman GA,** Hanashiro PK. Reversal of tricyclic-antidepressant-induced cardiac conduction abnormalities by phenytoin. *Ann Emerg Med* 1981;**10**:82—6.
61. **Cantrill S.** Prophylactic phenytoin in tricyclic overdose. *J Emerg Med* 1983;**1**:169—77.
62. **Perucca E,** Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* 1977;**4**:485—6.
63. **Shin J-G,** Park J-Y, Kim M-J, *et al*. Inhibitory effects of tricyclic antidepressants (TCAs) on human cytochrome P450 enzymes in vitro: mechanism of drug interaction between TCAs and phenytoin. *Drug Metab Dispos* 2002;**30**:1102—7.
64. **Callaham M,** Schumaker H, Pentel P. Phenytoin prophylaxis of cardiotoxicity in experimental amitriptyline poisoning. *J Pharmacol Exp Ther* 1988;**245**:216—20.
65. **Toxbase.** http://www.spib.axl.co.uk. 2007.
66. **Toxbase.** http://www.spib.axl.co.uk. 2007.
67. **Barnes RJ,** Kong SM, Wu RWY. Electrocardiographic changes in amitriptyline poisoning. *BMJ* 1968;**3**:222—3.
68. **Freeman JW,** Mundy GR, Beattie RR, *et al*. Cardiac abnormalities in poisoning with tricyclic antidepressant. *BMJ* 1969;**2**:610—11.
69. **Masters AB.** Delayed death in imipramine poisoning. *BMJ* 1967;**3**:866—7.
70. **McAlpine SB,** Calabro JJ, Robinson MD, *et al*. Late death in tricyclic antidepressant overdose revisited. *Ann Emerg Med* 1986;**15**:1349—52.
71. **Chan B,** Gaudry P, Grattan-Smith TM, *et al*. The use of Glasgow Coma Scale in poisoning. *J Emerg Med* 1993;**11**:579—82.
72. **Unverir R,** Atilla R, Karcioglu O, *et al*. A retrospective analysis of antidepressant poisonings in the emergency department: 11-year experience. *Hum Exp Toxicol* 2006;**25**:605—12.
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, and a sign of circulatory insufficiency on arrival. *Am J Emerg Med* 2007;**25**:757—61.
74. **Dawling S,** Crome P, Braithwaite R. Effect of delayed administration of activated charcoal on nortriptyline absorption. *Eur J Clin Pharmacol* 1978;**14**:445—7.
75. **Scheinin M,** Virtanen R, lisalo E. Effects of single and repeated doses of activated charcoal on the pharmaokinetics of doxepin. *Int J Clin Pharmacol Ther Toxicol* 1985;**24**:326—32.
76. **Crome P,** Dawling S, Braithwaite RA. Effect of activated charcoal on the absorption of nortriptyline. *Lancet* 1977;**8050**:1203—5.
77. **Crome P,** Adams R, Ali C. Activated charcoal in tricyclic antidepressant poisoning: pilot controlled clinical trial. *Hum Toxicol* 1983;**2**:205—9.
78. **Karkkainen S,** Neuvonen PJ. Pharmacokinetics of amitriptyline influenced by oral charcoal and urinary pH. *Int J Clin Pharmacol* 1986;**24**:326—32.
79. **Swartz CM,** Sherman A. The treatment of tricyclic antidepressant overdose with repeated charcoal. *J Clin Psychopharmacol* 1984;**4**:336—40.
80. **Ilett KF,** Hackett LP, Dusci LJ, *et al*. Disposition of dothiepin after overdose: effects of repeated-dose activated charcoal. *Ther Drug Monit* 1991;**13**:485—9.
81. **Bailey B,** Buckley NA, Amre DK. A meta-analysis of prognostic indicators to predict seizures, arrhythmias or death after tricyclic antidepressant overdose. *J Toxicol Clin Toxicol* 2004;**42**:877—88.
82. **Eizadi-Mood N,** Moein N, Saghaei M. Evaluation of relationship between arterial and venous blood gas values in the patients with tricyclic antidepressant poisoning. *Clin Toxicol (Phila)* 2005;**43**:357—60.
83. **Brown TC,** Barker GA, Dunlop ME, *et al*. The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. *Anaesth Intensive Care* 1973;**1**:203—10.
84. **Brown TC.** Sodium bicarbonate treatment for tricyclic antidepressant arrhythmias in children. *Med J Aust* 1976;**2**:380—2.
85. **Koppel C,** Wiegreffe A, Tenczer J. Clinical course, therapy, outcome and analytical data in amitriptyline and combined amitriptyline/chlordiazepoxide overdose. *Hum Exp Toxicol* 1992;**11**:458—65.
86. **Teba L,** Scheibel F, Dedhia H, *et al*. Beneficial effect of norepinephrine in the treatment of circulatory shock caused by tricyclic antidepressant overdose. *Am J Emerg Med* 1988;**6**:566—8.
87. **Vernon DD,** Banner W, Garrett J, *et al*. Efficacy of dopamine and norepinephrine for the treatment of haemodynamic compromise in amitriptyline intoxication. *Crit Care Med* 1991;**19**:544—9.
88. **Knudsen K,** Abrahamsson J. Effects of epinephrine, norepinephrine, magnesium sulfate, and milrinone on survival and the occurrence of arrhythmias in amitriptyline poisoning in the rat. *Crit Care Med* 1994;**22**:1851—5.
89. **Knudsen K,** Abrahamsson J. Epinephrine and sodium bicarbonate independently and additively increase survival in experimental amitriptyline poisoning. *Crit Care Med* 1997;**25**:669—74.
90. **Knudsen K,** Abrahamsson J. Effects of epinephrine and norepinephrine on hemodynamic parameters and arrhythmias during a continuous infusion of amitriptyline in rats. *Clin Toxicol* 1993;**31**:461—71.
91. **Ruddy JM,** Seymour JL, Anderson NG. Management of tricyclic antidepressant ingestion in children with special reference to the use of glucagon. *Med J Aust* 1972;**1**:630—3.
92. **Sener EK,** Gabe S, Henry JA. Response to glucagon in imipramine overdose. *J Toxicol Clin Toxicol* 1995;**33**:51—3.
93. **Sensky PR,** Olczak SA. High dose intravenous glucagon in severe tricyclic poisoning. *Postgrad Med J* 1999;**75**:611—12.
94. **Citak A,** Soysal DD, Ucsel R, *et al*. Efficacy of long duration resuscitaiton and magnesium sulphate treatment in amitriptyline poisoning. *Eur J Emerg Med* 2002;**9**:63—6.
95. **Minton NA,** Goode AG, Henry JA. The effect of a lipid suspension on amitriptyline disposition. *Arch Toxicol* 1987;**60**:467—9.
96. **Greenland P,** Howe TA. Cardiac monitoring in tricyclic antidepressant overdose. *Heart Lung* 1981;**10**:856—9.
97. **Pentel P,** Sioris L. Incidence of late arrhythmias following tricyclic antidepressant overdose. *Clin Toxicol* 1981;**18**:543—8.
98. **Goldberg RJ,** Capone RJ, Hunt JD. Cardiac complications following tricyclic antidepressant overdose. *JAMA* 1985;**254**:1772—5.
99. **Emerman C,** Connors AF, Burma GM. Level of consciousness as a predictor of the complications following tricyclic overdose. *Ann Emerg Med* 1987;**16**:326—30.
100. **Tokarski GF,** Young MJ. Criteria for admitting patients with tricyclic antidepressant overdose. *J Emerg Med* 1988;**6**:121—4.
101. **Banahan B,** Schelkun P. Antidepressant overdose: conservative management in the community hospital with cost saving implications. *J Emerg Med* 1990;**8**:451—4.
102. **Hulten BA,** Adams R, Askenasi R, *et al*. Predicting severity of tricyclic antidepressant overdose. *J Toxicol Clin Toxicol* 1992;**30**:161—70.

APPENDIX 1: RELEVANT PAPERS

Table A1 Assessing the need for intubation in semiconscious patients presenting to the ED following psychotropic drug overdose

Author date, country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Chan *et al*, 1993, Australia[71]	Retrospective analysis	393 patients who presented to the ED with a history or evidence of overdose (of a drug with no antidote) who had GCS documented at presentation	GCS ≤8/15 for prediction of intubation	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	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
			Relationship between GCS and intubation (logistic regression analysis)	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)	

Continued

Table AI Continued

Author date, country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Emerman *et al*, 1987, USA[29]	Retrospective analysis	All 92 patients age ≥17 years who were admitted to Clevel and Metropolitan General Hospital with TCA overdose between 1975 and 1985	Association between GCS and complications (hypoventilation, loss of protective airway reflexes, hypotension, seizures, haemodynamically significant arrhythmias or death	Significant association ($p<0.001$). GCS was significantly better than QRS interval ($p<0.001$)	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
			GCS ≤8 for prediction of serious complications	Sensitivity 89%, specificity 88%. GCS ≤8 was significantly more sensitive than QRS ≥100 ms ($p<0.05$)	
			Sensitivity of GCS ≤8 for prediction of individual complications	Hypoventilation or loss of protective airway reflexes: 86.5%. Death, hypotension, seizures, haemodynamically significant arrhythmias: 100%	
			Logistic regression model for prediction of complications	Only GCS was a significant independent predictor of complications	
Hulten *et al*, 1992, Sweden[28]	Prospective diagnostic cohort study	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	Matthew-Lawson coma grade ≥3 for prediction of serious complications (seizures, hypotension (systolic BP <100 mmHg), arrhythmias, need for intubation)	Sensitivity 65%, specificity 94%	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
			Matthew-Lawson coma grade ≥2 for prediction of serious complications	Sensitivity 81%, specificity 77%	
			Matthew-Lawson coma grade versus QRS duration and plasma TCA level for prediction of serious complications	Matthew-Lawson coma grade was the strongest predictor in logistic regression model. QRS duration >100 ms was more sensitive for prediction of complications (86%) but less specific (75%)	
Liisanantti *et al*, 2003, Finland[30]	Retrospective analysis	257 patients admitted to ICU with self-poisoning of psychopharmaceutical drugs between November 1989 and October 2000. Classed as conscious (GCS 8—15) or unconscious (3—7) based on 'approximate GCS'. 73 patients (28.4%) met criteria for aspiration pneumonia	Unconsciousness on discovery for prediction of aspiration pneumonia	OR 2.9 (95% CI 1.2 to 7.0)	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
			Unconsciousness in ED for prediction of aspiration pneumonia	OR 2.2 (95% CI 0.9 to 5.4)	
			Unconscious when found and intubated on discovery for prediction of aspiration pneumonia	OR 1.8 (95% CI 0.6 to 5.7)	
			Unconscious when found and intubated in ED for prediction of aspiration pneumonia	OR 3.4 (95% CI 1.3 to 8.7)	
			Unconscious when found and intubated in ICU for prediction of aspiration pneumonia	OR 3.5 (95% CI 1.1 to 10.7)	
			Mean length of hospital stay	Aspiration pneumonia 6.5 days (95% CI 5.3 to 7.6); no aspiration pneumonia 2.8 days (2.5—3.1)	
			Mean length of ICU stay	Aspiration pneumonia 1.9 days (1.3—2.6); no aspiration pneumonia 0.9 days (0.8—0.9)	
Unverir *et al*, 2006, Turkey[72]	Retrospective analysis	356 patients who presented to the ED with antidepressant ingestion between 1993 and 2004	Relationship between GCS and intubation rates	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 >8	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
			Logistic regression model for prediction of the need for intubation	GCS the strongest independent predictor of need for intubation (OR 29.4, 95% CI 8.1 to 106.4). Presence of seizures was also an independent predictor of intubation. Age, gender and QRS prolongation were not independent predictors	

Continued

Table AI Continued

Author date, country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Yanagawa *et al*, 2006, Japan[73]	Retrospective analysis	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)	Mean GCS (on arrival) in early and late groups Logistic regression model for prediction of 'late' extubation (>2 days)	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)	Retrospective. Significant selection bias: only intubated patients included. No analysis of different GCS cut-offs for prediction of late extubation

ED, emergency department; GCS, Glasgow Coma Score; TCA, tricyclic antidepressant.

Table AII Single dose activated charcoal in tricyclic antidepressant (TCA) overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Bosse *et al*, 1995, USA[34]	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	PRCT	Mean serum TCA levels	No significant differences (p=0.797)	Block randomisation No sample size calculation — unknown power
			Seizures	No significant difference (p=1.000)	
			Wide QRS (>0.1 s)	No significant difference (p=0.472)	
			Hypotension (≤90 systolic)	No significant difference (p=0.874)	
			Sinus tachycardia (rate >100)	No significant difference (p=0.280)	
			Ventricular dysrhythmias	None in any group	
			Median GCS	Mean 8.5 in group 1; 8 in group 2; 12 in group 3 (p=0.242)	
			Mean length of stay in hospitalised patients	No significant difference (p=0.473)	
			Mean length of ICU stay	No significant difference (p=0.436)	
			Mean duration of sinus tachycardia	No significant difference (p=0.594)	
			Incidence of aspiration	15.7% of patients aspirated (no difference between groups, p=0.501)	
Dawling *et al*, 1978, UK[74]	6 fasted healthy volunteers given 75 mg nortriptyline, allocated to four groups on different occasions: (1) No treatment (2) 10 g Medicoal after 30 min (3) 10 g Medicoal after 2 h (4) 10 g Medicoal after 4 h	Experimental, volunteer study, crossover design	Mean reduction in peak plasma nortriptyline concentrations	77% in group (2), 37% in group (3), 19% in group (4) (p<0.001)	Conducted in fasted volunteers. Small dose of nortriptyline
			Mean reduction in plasma nortriptyline availability (area under time-concentration curve)	74% in group (2), 37.5% in group (3), 13% in group (4) (p<0.001)	
Hedges *et al*, 1986, USA[33]	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	Prospective observational cohort	Correlation between estimated plasma amitriptyline concentration half-life and time to charcoal	Directly proportional (r=0.78, p<0.05)	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
			Correlation between estimated plasma amitriptyline concentration half-life and dose of charcoal	Weak inverse correlation (r=0.44, p=0.25)	
Scheinin *et al*, 1985, Finland[75]	Eight healthy volunteers given 50 mg doxepin followed by 15 g activated charcoal after 30 min	Experimental, volunteer study	Peak serum doxepin concentration	Reduced by 70%	Volunteer study, small numbers. Small dose of TCA and charcoal
			Total doxepin availability	Reduced by 49%	
			Apparent elimination half-life of doxepin and its metabolite	Prolonged by 350% and 140% respectively following single dose charcoal	
Crome *et al*, 1977, UK[76]	Healthy volunteers given 75 mg nortriptyline. Control session: no intervention. Treatment session: 10 g Medicoal at 30 min. Plasma nortriptyline levels measured after 2, 4, 6, 10, 24, 32 and 48 h	Experimental, crossover design	Plasma nortriptyline level	60% (range 30–81%) average reduction in peak levels (p=0.01)	Small dose of TCA and charcoal. Study in fasted volunteers. The results cannot be directly extrapolated to the population with TCA overdose

Continued

Table AII Continued

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Crome *et al*, 1983, UK[77]	48 patients with suspected TCA overdose. All had gastric lavage. 10 g Medicoal versus nothing	PRCT	Plasma TCA concentration Clinical signs	No difference in rate of fall noted No significant difference	Small numbers with complications. Small charcoal dose. 18 patents excluded. Time from ingestion to charcoal not investigated. No data on numbers also given gastric lavage
Karkkainen and Neuvonen, 1986[78]	Six healthy volunteers. Each took 75 mg amitriptyline. 50 g charcoal within 5 min	Experimental	Plasma TCA bioavailability (area under the concentration-time curve)	Decreased by 99% compared with controls	Small dose of TCA. Unrealistic time to charcoal
Hulten *et al*, 1988, multinational[35]	77 patients >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)	PRCT	Plasma TCA concentration Toxic symptoms	No significant difference in peak or half-life Fewer in control group (not statistically significant)	Control group differed from charcoal group at baseline. No data regarding the timing of charcoal administration

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

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Crome, 1977, UK[76]	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	PRCT	% Reduction in peak plasma levels % Reduction nortriptyline availability	Multidose > single dose (72% reduction vs 58%), $p<0.05$ Multidose > single dose (70% reduction vs 55%), $p<0.05$	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
Schwartz *et al*, 1984, USA[79]	Three randomly selected patients with amitriptyline overdose. Gastric lavage performed. Given 40—50 g activated charcoal followed by 20—25 g activated charcoal repeatedly via nasogastric tube	Observational	Half-life	Reduced half-life below 10 h for each patient to as low as 4 h	Only half-life measured. No control group. Very small number
Scheinin *et al*, 1985, Finland[75]	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	Non-randomised controlled trial	Total plasma clearance (doxepin) Half life (desmethyldoxepin) Half-life (doxepin)	Repeated dose >clearance than control. Repeated dose >single dose (significance not available) Repeat dose (16.2±2.3) < single dose (80.6±20.5) ($p<0.05$) Repeat dose (20.7±3.1) < single dose (67.9±12.9) ($p<0.01$)	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. Received charcoal after 30 min, in clinical setting not many patients will receive charcoal within 30 min, hence can this be applied to the clinical setting of an emergency department?
Karkkainen *et al*, 1986[78]	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	PRCT	Half-life	Reduced half-life by 20% from 27.4±(SE) 4.8 h (control) to 21.1±3.3 h (charcoal group)	Small number. Volunteers used, hence difficult to apply result to clinical setting
Ilett *et al*, 1991[80]	Three patients with dothiepin overdose treated with repeated activated charcoal	Observational study	Mean half-life	12.1±1.3 h compared to literature range of 18.5—24 h.	Small number. No control group

Table AIV Gastric lavage following tricyclic antidepressant (TCA) overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Hulten *et al*, 1988, Sweden[35]	91 patients with suspected TCA overdose. 43 gastric lavage only, 34 gastric lavage + 20 g activated charcoal	PRCT	Peak plasma concentrations	No difference	Only 20 g of charcoal used. All patients received gastric lavage as standard (no comparison of charcoal vs lavage)
			Plasma half-lives	No difference	
			Plasma drug concentration versus time curve	No difference	
			Toxic symptoms	Toxic symptoms greater in gastric lavage only group but this was not statistically significant	
Bosse *et al*, 1995, USA[34]	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)	PRCT	Mean length of stay in hospital (h)	No significant difference (1) 93.3; (2) 107.2; (3) 66.7 (p=0.473)	Not blinded. Small numbers. Variations between presenting GCS and drug levels between groups
			Mean length of stay in ICU (h)	No significant difference (1) 66.9; (2) 54.1; (3) 34.4 (p=0.436)	
			Mean duration sinus tachycardia (h)	No significant difference (1) 20.8; (2) 30.8; (3) 32.2 (p=0.594)	
			Mean mechanical ventilation time (h)	No significant difference (1) 43.4; (2) 24.1; (3) 17.8 (p=0.321)	
			Aspiration	No significant difference (1) 2/22; (2) 3/14; (3) 15/3 (p=0.501)	

GCS, Glasgow Coma Score.

Table AV ECG and serum drug levels for predicting complications

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Bailey *et al*, 2004[81]	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 >0.10 s; (3) QTc >430 ms; (4) R/S ratio >0.7; (5) right axis deviation of 120–270° in terminal 40 ms frontal plane QRS vector (T40)	Systematic review and meta-analysis	Number of studies	941 studies found, 18 studies included in the review	All but one studies retrospective, most non-blinded, time between ingestion and measurement not reported
			Pooled sensitivity and specificity to predict death	QRS=0.81 and 0.62; TCA concentration = 0.76 and 0.60; QTc= 0.50 and 0.68; T40=0.33 and 0.71, respectively	
			Pooled sensitivity and specificity to predict seizures	QRS=0.69 and 0.69; TCA concentration = 0.75 and 0.72; T40=0.50 and 0.72, respectively	
			Pooled sensitivity and specificity to predict ventricular arrhythmias	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	
			Positive and negative likelihood ratios for death	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	
			Positive and negative likelihood ratios for seizures	QRS= 3.18 and 0.38; TCA concentration = 2.39 and 0.46; T40= 1.79 and 0.69, respectively	
			Positive and negative likelihood ratios for ventricular arrhythmias	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; QTc=1.77 and 0.39; R/S ratio=15.7 and 0.55, respectively	

TCA, tricyclic antidepressant.

Table AVI Venous versus arterial blood gas sampling

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Eizadi-Mood *et al*, 2005, Iran[82]	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	Prospective diagnostic cohort study	Mean (SD) pH on admission	Venous 7.34 (0.0049); arterial 7.37 (0.0052) (p=0.00)	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
			Mean (SD) HCO_3 30 min after bicarbonate	Venous 25.24 (3.35); arterial 23.78 (3.11) (p=0.23)	
			Mean (SD) pH 30 min after bicarbonate	Venous 7.34 (0.049); arterial 7.37 (0.042) (p=0.12)	
			Mean (SD) PCO_2 on admission	Venous 43.79 (6.39); arterial 38.47 (7.10) (p=0.00)	
			Mean (SD) PO_2 on admission	Venous 42.50 (10.78); arterial 79.94 (15.94) (p=0.00)	
			Mean (SD) HCO_3 on admission	Venous 23.26 (3.23); arterial 22.19 (3.28) (p=0.01)	
			Linear regression model (arterial and venous pH measurements)	Significant relationship (p<0.001). r^2=0.60	

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

Table AVII Sodium bicarbonate following tricyclic antidepressant (TCA) overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Brown *et al*, 1973, Australia[83]	4 children aged 18 months to 3 years	Case series	Blood pressure Reversion of dysrhythmias to sinus rhythm	Normalised Normalised	Case series only. Causal relationship between sodium bicarbonate and clinical improvement not established
Brown, 1976, Australia[84]	12 children aged 15 months to 12 years with arrhythmias. Sodium bicarbonate 0.5–2 mEq/kg	Case series	Reversion of dysrhythmias to sinus rhythm	9/12 reverted to sinus rhythm	Case series only. Causal relationship between sodium bicarbonate and clinical improvement not established
Koppel *et al*, 1992, Germany[85]	184 cases of overdose. 8 patients with cardiac disturbance. 100 mmol sodium bicarbonate administered	Retrospective cohort study	Rhythm	4/8 reverted to sinus rhythm	Small numbers. No comparison with control group. In some cases, mixed overdose with chlordiazepoxide
Hoffmann *et al*, 1993, USA[50]	91 patients with overdose. Sodium bicarbonate to pH of 7.55	Retrospective cohort study	Blood pressure QRS prolongation (>0.11 s)	20/21 normalised (>90 mm Hg systolic) 39/49 improved	No adequate control group. Physicians not blinded. Data may be missing from notes since retrospective study

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

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Teba *et al*, 1988, USA[86]	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	Case report	Systemic systolic BP (SBP)	Case 1: Continuous infusion of norepinephrine increased SBP from 68 mm Hg to >100 mm Hg. Case 2: Following norepinephrine infusion SBP increased from 52 mm Hg to 130 mm Hg	Only 2 case reports. These may be exceptional cases
Vernon *et al*, 1991, USA[87]	15 dogs infused with amitriptyline HCl. Received dopamine 5, 15 and 30 μg sequentially or norepinephrine 0.25, 0.5 and 1.0 μg sequentially. Haemodynamic measurements after each dose	Experimental randomised controlled trial	Mean arterial pressure (MAP) (mm Hg)	All doses of norepinephrine > MAP compared with control ($p<0.05$). Two higher dopamine doses > MAP compared with control ($p<0.05$). At highest dose, no significant difference between norepinephrine and dopamine	Animal study. Not blinded. Randomisation questionable. Small number. Each catecholamine infusion given sequentially
			Cardiac output (CO) (l/min)	All doses of norepinephrine > CO than control ($p<0.05$). Two higher dopmaine doses > CO than control ($p<0.05$). At highest dose, no significant difference between norepinephrine and dopamine	
			Peak left ventricular (LV) dP/dt (rate of change of LV pressure)	All doses of norepinephrine > LV dP/dt than control ($p<0.05$). Two higher dopamine doses > LV dP/dt than control ($p<0.05$). At highest dose, no significant difference between norepinephrine and dopamine	
			Mixed venous oxygen saturation (SVO_2)	All doses of norepinephrine > SVO_2 than control ($p<0.05$). Two higher dopamine doses > LV SVO_2 than control ($p<0.05$). At highest dose, no significant difference between norepinephrine and dopamine	
			Systemic vascular resistance (SVR)	All doses of norepinephrine > SVP than control ($p<0.05$). At highest dose, no significant difference between norepinephrine and dopamine	

Continued

Table AVIII Continued

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Knudsen and Abrahamsson, 1994, Sweden[88]	86 male Wistar rats infused with amitriptyline HCl. Treated with: epinephrine; norepinephrine; epinephrine + magnesium; norepinephrine + magnesium; Milrinone	Non-randomised controlled intervention trial	Survival	Epinephrine + norepinephrine > survival than control ($p<0.001$). Epinephrine > norepinephrine survival rate	Animal study: can it be useful in humans? Not blinded. Small number. Raw data absent in some measurements
			Increase in QRS duration	Epinephrine significantly lower increase in QRS compared with control + norepinephrine groups	
			Onset arrhythmia	Epinephrine delayed onset of arrhythmias compared with control ($p<0.01$)	
			Duration sinus rhythm	Epinephrine > control ($p<0.01$) Epinephrine > norepinephrine ($p<0.05$)	
Knudsen and Abrahamsson, 1997, Sweden[89]	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)	Non-randomised, animal controlled intervention trial	Survival	Epinephrine + sodium bicarbonate > survival rate than other groups ($p<0.01$). Epinephrine treatment groups > survival rates than norepinephrine treatment groups ($p<0.01$). Treatment groups > survival rate than control groups ($p<0.01$). Epinephrine + sodium bicarbonate treatment > survival rate than epinephrine alone ($p<0.01$). Norepinephrine + sodium bicarbonate treatment > survival rate than norepinephrine alone ($p<0.01$)	Animal study hence extrapolation to humans may be difficult. Not blinded. Raw data unavailable in some measurements
			Arrhythmias	Epinephrine-treated rats had a longer time to onset of arrhythmias than norepinephrine-treated rats (21.5 vs 11.6 min) ($p<0.05$). Epinephrine + sodium bicarbonate-treated rats had the longest time in sinus rhythm	
			QRS duration	Epinephrine treatment associated with shorter QRS interval than norepinephrine treatment ($p<0.05$)	
Knudsen and Abrahamsson, 1993[90]	101 male Wistar rats poisoned with amitriptyline given 0.1, 0.5 or 5.0 mg/kg/min epinephrine or norepinephrine. Control group received glucose infusion	Non-randomised, animal controlled intervention trial	Mean arterial pressure (MAP)	All doses of norepinephrine and two higher doses of epinephrine increased MAP. Norepinephrine > epinephrine at low and intermediate doses	Animal study: difficult to apply data to humans. Experiment not blinded. Raw data absent from study. No significant difference between treatment according to Fisher exact test
			Mortality at 75 min (%)	Control group=75%; norepinephrine=45%; epinephrine=27%. At intermediate dose, epinephrine group had lowest death risk ($p=0.012$)	
			Arrhythmia	Intermediate dose: norepinephrine > arrhythmia than epinephrine ($p<0.05$)	

Table AIX Glucagon to treat haemodynamic instability after tricyclic antidepressant (TCA) overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Ruddy *et al*, 1972, Australia[91]	4-year-old ingested approx 1000 mg imipramine, episode of PEA 1.5 h duration	Case report	Cardiac status	Improved with 1 mg boluses glucagon	Case report. Patient also received pyridostigmine, sodium bicarbonate, isoprenaline, digoxin, lidocaine and mannitol
Sener *et al*, 1995, UK[92]	25 year-old woman. Plasma toxicology: imipramine 3.0 mg/l, desipramine 0.18 mg/l, diazepam 2.9 mg/l, nordiazepam 2.2 mg/l, chlorpromazine 0.3 mg/l, temazepam 0.25 mg/l	Case report	Blood pressure Cardiac rhythm	No response to 1 mg bolus glucagon. 40 mm Hg systolic rise after glucagon No response to 1 mg bolus glucagon. Broad complex reverted to sinus after 10 mg bolus	Multiple drugs ingested in overdose. Patient also received sodium bicarbonate, phenytoin and isoprenaline and fluid resuscitation
Sensky *et al*, 1999, UK[93]	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, nordiazepam 0.12 mg/l	Case report	Blood pressure Cardiac rhythm	No response to 1 mg bolus glucagon. 30 mm Hg systolic rise after glucagon No response to 1 mg bolus glucagon. Broad complex reverted to sinus after 10 mg bolus	Case report. Multiple drugs ingested in overdose Patient also received N-acetylcysteine, epinephrine, norepinephrine, ephedrine, dobutamine and aminophylline with fluid restriction

OD, overdose PEA, pulseless electrical activity.

Table AX Magnesium sulphate to treat dysrhythmias following TCA overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Knudsen and Abrahamsson, 1997, Sweden[53]	44-year-old woman admitted after an overdose of amitriptyline. She suffered a cardiac arrest (ventricular fibrillation) after 12 h	Case study	Observed effect of cardiopulmonary resuscitation, sodium bicarbonate, defibrillation (four attempts), lidocaine and epinephrine ('several doses') Observed effect of magnesium sulphate 20 mmol $\times$2 and further defibrillation	Patient remained in ventricular fibrillation Spontaneous return of circulation; 'stable regular heart rhythm'. Haemodynamic performance normalised	Only a case study. Observed effects may or may not have been partly due to the effect of magnesium sulphate
Citak *et al*, 2002, Turkey[94]	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)	Case study	Observed effect of lidocaine, bicarbonate and attempted electrical cardioversion Observed effect of magnesium sulphate	No effect Cardiac rhythm normalised without side effects	Case study. Observed effects may or may not have been partly due to the effects of magnesium sulphate
Sarisoy *et al*, 2007, Turkey	4-year-old boy who had taken 70 mg/kg amitriptyline Glasgow Coma Score 3/15, bradycardia and hypotension on arrival. Cardiac arrest (VF) despite epinephrine, bicarbonate, lidocaine and normal saline. VT after 'synchronised cardioversion' of VF. Then loaded with 2 g magnesium sulphate followed by infusion of 3 mg/min	Case report	Reversion of VT	After magnesium infusion, 'normal cardiac rhythm' was obtained	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

Table AXI Lipid emulsion for treatment of TCA toxicity

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Minton *et al*, 1987, UK[95]	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	Prospective crossover randomised controlled volunteer study	Mean levels of amitriptyline + nortriptyline Mean triglyceride concentration	13.8% higher at the end of lipid treatment compared with saline group ($p>0.05$) 500% increase in lipid emulsion group ($p<0.005$)	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

Table AXII Observation of asymptomatic patients following tricyclic antidepressant (TCA) overdose

Author, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Greenland and Howe, 1981, USA[96]	62 patients with TCA overdose	Retrospective cohort study	Cardiac arrhythmias	No cardiac arrhythmias occurred after the first 24 h in any patient free of such complication earlier	Lack of raw data; important details may be missing in retrospective study
Pentel and Sioris, 1981, USA[97]	Patients with TCA overdose. All underwent gastric emptying	Retrospective cohort study	Development of complications	All patients who developed complications did so within 1 h of hospitalisation. No patients developed arryhthmias after being alert and having a normal ECG for 1 h.	Does not mention the exact number of patients in the study. Vital data may be missing from notes due to retrospective study
Goldberg *et al*, 1985, USA[98]	75 patients with TCA overdose	Retrospective cohort study	Cardiac complications	No new complications after 24 h	Data may be missing due to retrospective study. No actual data on times of complications following overdose
Emerman *et al*, 1987, USA[99]	92 patients with TCA overdose admission from 1975 to 1985	Retrospective cohort study	Development of complications (26/37 patients had documentation)	19/26 developed complications within 30 min. 7/26 developed complications between 30 and 120 min	Data may be missing due to retrospective study
Tokarski and Young, 1988, USA[100]	Review of 45 patients with TCA overdose from 1982 to 1985 and algorithm applied	Retrospective cohort study	Patient discharged using algorithm (no major signs toxicity/QRS $<$0.10 in 6 h)	20 patients would have been discharged since no signs of major toxicity or QRS was $<$0.10 s within 6 h of admission. None of these patients developed any complications	Small sample. Retrospective study, hence vital data from notes may be missing
Banahan and Schelkun, 1990, USA[101]	Review of 33 patients with an admission diagnosis of TCA overdose between January 1985 and December 1988. Tokarski and Young algorithm applied (see above)	Retrospective cohort study	Patients discharged under algorithm by Tokarski and Young (see above)	11 patients did not show signs of major toxicity or QRS $>$0.10 s within 6 h. Using the algorithm, these patients could been discharged. None developed any complications	Small sample. Retrospective study, hence data may be missing
Hulten *et al*, 1992, Sweden[102]	67 patients with TCA overdose	Cohort study	Development of complications	All patients who developed complications did so within 6 h of admission	Lack of raw data. No sample size estimation performed

APPENDIX 2: SEARCH FILTERS

TCA filter
(exp Antidepressive Agents, Tricyclic/OR tricyclic.mp. OR amitriptyline.mp. OR exp Amitriptyline/OR desipramine.mp. OR exp Desipramine/OR clomipramine.mp. OR exp Clomipramine/OR doxepin.mp. OR exp Doxepin/ OR dothiepin.mp. OR exp Dothiepin/ 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 Nitrazepam/OR (benzodiazepin$ OR diazepam OR clonazepam OR nitrazepam OR clonazepam OR midazolam OR temazepam).mp.

Phenytoin filter
(exp Phenytoin OR phenytoin.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.)

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

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