**Clinical question.**

"In adults with severe cardiovascular or life-threatening toxicity (prehospital or in-hospital) due to cyclic antidepressants (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival, neurologically-intact survival)?"

Clinical question revised as per workgroup conference call.

Standard care (C), as per the treatment algorithm, is defined as the following: Sodium bicarbonate, hyperventilation, normal saline bolus (0.5 to 1.0 L), magnesium sulfate, lidocaine, epinephrine or other alpha or beta agonists.

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention/Therapy

**State if this is a proposed new topic or revision of existing worksheet:** New

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

PubMed, yield 37 hits: Search for combinations of MeSH terms (“heart arrest” or “arrhythmias, cardiac” or “signs and symptoms, respiratory” or “emergencies” or “overdose”) and (“antidepressive agents, tricyclic”) and (“emergency treatment” or “intratracheal intubation” or “respiration, artificial” or “antidote”) or (“tricyclic” and “antibody” and “overdose”) or (“tricyclic” and “antibody” and “antidote”). Limits: English language publications with abstracts, adult studies.

TOXNET/Toxline, yield 19 hits: Search for combinations of terms tricyclic, antidepressant, toxicity, emergency.

Central Register of Controlled Trials, yield 4548 hits: Search for the terms tricyclic, amitriptyline, overdose, toxicity.

EMBASE, yield 82 hits: Search for combinations of terms tricyclic, antidepressant, toxicity, emergency

AHA Master Library: Search for the terms tricyclic, antidepressant

Manual search of references from current guidelines, articles, and textbooks.

- **State inclusion and exclusion criteria**
  - Inclusion criteria: Scientific papers assessing a specific intervention for resuscitation of the patient with severe or life-threatening tricyclic poisoning.
  - Exclusion criteria: Single case reports, review papers, position statements, published guidelines, non-adult studies.

- **Number of articles/sources meeting criteria for further review:**


  No additional articles found in TOXNET/Toxline, Central Register of Controlled Trials, or EMBASE.

### Summary of evidence

#### Evidence Supporting Clinical Question

<p>| Good | | | Hoffman 1993, 336 B,C,E |
|------|-----------------------------|-----------------------------|
|      | Teba 1988, 566 B,C,D,E | Nattel 1984, 430 B,E |
|      | | | Nattel 1984, 83 B,E |</p>
<table>
<thead>
<tr>
<th>Evidence Neutral to Clinical Question</th>
<th>Evidence Opposing Clinical Question</th>
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<tbody>
<tr>
<td><strong>Level of evidence</strong></td>
<td><strong>Level of evidence</strong></td>
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<tr>
<td>A = Return of spontaneous circulation</td>
<td>A = Return of spontaneous circulation</td>
</tr>
<tr>
<td>C = Survival to hospital discharge</td>
<td>C = Survival to hospital discharge</td>
</tr>
<tr>
<td>E = Other endpoint</td>
<td>E = Other endpoint</td>
</tr>
<tr>
<td>B = Survival of event</td>
<td>D = Intact neurological survival</td>
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<tr>
<td><em>Italics</em> = Animal studies</td>
<td><em>Italics</em> = Animal studies</td>
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**Evidence Neutral to Clinical Question**

| Good |  |  |  | Callaham 1988, 216 B,E |
|------|  |  |  | **Fair**                |
|      |  |  |  | Barrueto 2005, 147 B |
|      |  |  |  | Knudsen 1994, 494 B,E |
|      |  |  |  | Tobis 1980, 602 E      |
|      |  |  |  | **Poor**               |
|      |  |  |  | Mayron 1985, 876 B,E   |

**Evidence Opposing Clinical Question**

| Good |  |  |  |  |
|------|  |  |  | **Fair**                |
|      |  |  |  | Newton 1975, 941 B,E    |
|      |  |  |  | **Kline 1994, 224 E**   |
|      |  |  |  |  |
|      |  |  |  | **Poor**               |
|      |  |  |  | Pentel 1980, 588 A,B,E  |

**REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

**Key Points Based on Available Literature:**

**Sodium Bicarbonate:** Two large case series (LOE 4) [Hoffman, 1993, 336; Koppel, 1992, 458], 1 in-vitro study (LOE 5) [Sasyniuk, 1986, 1052], and 7 animal studies (LOE 5) [Brown, 1976, 255; Hedges, 1985, 253; Knudsen, 1997, 669; Nattel, 1984, 430; Pentel, 1984, 12; Sasyniuk, 1986, 1052] support the use of sodium bicarbonate in the treatment of tricyclic antidepressant induced dysrhythmias. One small case series (LOE 4) [Pentel, 1980, 588], supports the use of sodium bicarbonate in the setting of cardiac arrest.

**Hyperventilation:** One short case series (LOE 4) [Bessen, 1985, 537] and 1 animal study (LOE 5) [Nattel, 1984, 430] support the use of hyperventilation in the treatment of tricyclic induced dysrhythmias.

**Antidyssrhythmics:** Evidence for use of other specific antidysrhythmic (lidocaine, magnesium, amiodarone) is equivocal at best. (LOE 5) [Knudsen, 1994, 494; Nattel, 1984, 430; Knudsen, 1994, 1851; Knudsen, 1994, 494; Kline, 194, 224; Barrueto, 2005, 147]. Case series support the use of phenytoin for tricyclic induced dysrhythmias (LOE 4) [Hagerman, 1981, 82], however animal studies were neutral as to any benefit (LOE 5) [Callaham, 1988, 216; Mayron, 1986, 876].
Vasopressors: A retrospective study (LOE 3) [Tran, 1997, 864], case series (LOE 4) [Tobis, 1980, 602], and animal studies (LOE 5) [Knudsen, 1994, 1851; Vernon, 1991, 544] support the use of norepinephrine for tricyclic induced hypotension; animal studies support the use of epinephrine (LOE 5) [Knudsen, 1993, 461; Knudsen, 1994, 1851; Knudsen, 1997, 669], dopamine (LOE 5) [Follmer, 1982, 424; Sangster, 1985, 407; Vernon, 1991, 544], and dobutamine (LOE 5) [Follmer, 1982, 424]. One small case series (LOE 4) [Pentel, 1980, 588], supports the use of epinephrine in the setting of cardiac arrest.

Benzodiazepines: One animal study demonstrated improved seizure control and mortality with the use of diazepam (LOE 5) [Follmer, 1982, 424].

Physostigmine: Use of physostigmine for tricyclic induced anticholinergic symptoms is both supported (LOE 4) [Johnson, 1976, 443; Koppel, 1992, 458] and opposed by case series (LOE 4) [Newton, 1975, 941; Pentel, 1984, 12].

Intralipid: Animal studies demonstrate a benefit to intralipid infusion in models of tricyclic toxicity (LOE 5) [Yoav, 2002, 30; Harvey, 2007, 178].

Anti-tricyclic Fab: Six animal studies demonstrate a benefit to anti-tricyclic Fab use in the treatment of varying degrees of tricyclic cardiotoxicity (LOE 5) [Brunn, 1992, 1392; Brunn, 1991, 841; Hursting, 1989, 53; Pentel, 1995, 334; Pentel, 1994, 387; Dart, 1996, 309]. One small human study provides evidence of safety and pharmacokinetic advantage, however clinical benefit is yet to be clearly demonstrated (LOE 4) [Heard, 2006, 275].

**Acknowledgements:** None

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**Citation List**

1. Barrueto F, Chuang A, Cotter BW, Hoffman RS, Nelson LS. Amiodarone fails to improve survival in amitriptyline-poisoned mice. *Clin Tox*. 2005;43:147-149. **Reviewer Summary:** An investigation of the effect of amiodarone pretreatment in amitriptyline toxicity using a mouse lethality model. Limitations include the difficulty of extrapolating results from a small animal model using the gross endpoint of death, and lack of electrophysiological and hemodynamic assessment. **Reviewer Conclusion:** The study demonstrated that there was no effect of amiodarone pretreatment on survival from amitriptyline poisoning in a mouse lethality model. Neutral, LOE 5, Quality Fair

2. Bessen HA, Niemann JT. Improvement of cardiac conduction after hyperventilation in tricyclic antidepressant overdose. *J Toxicol Clin Toxicol*. 1985;23:537-546. **Reviewer Summary:** Case series of three patients with amitriptyline poisoning, two with confirmatory levels. All three had QRS duration widening pre-hyperventilation. Post-hyperventilation all three demonstrated QRS narrowing. One patient also received intravenous sodium bicarbonate. Time between pre and post-hyperventilation EKG’s varied between 25 minutes and 4.5 hours. **Reviewer Conclusion:** The case series suggests that respiratory alkalination may be beneficial. However, the small number of patients confounding variables limits applicability as a sole or supplementary therapy as compared to standard therapy. Supporting, LOE 4, Quality Poor

3. Brown TC. Tricyclic antidepressant overdosage: experimental studies on the management of circulatory complications. *Clin Tox*. 1976;9:255-272. **Reviewer Summary:** Experimental dog study observing the antiarrhythmic effects of practolol, physostigmine, neostigmine, lignocaine, phenytoin, procainamide, potassium chloride, magnesium chloride, calcium gluconate, sodium bicarbonate, glucagon, and CI661, on amitriptyline induced arrhythmias. The study protocol was not clearly designed and there were no untreated controls. Endpoints for each intervention were not clearly defined, with several animals receiving multiple alternative drugs subsequent to the initial specified intervention. **Reviewer Conclusion:** Sodium bicarbonate was more efficacious than several alternate antiarrhythmics in controlling amitriptyline induced arrhythmias in a dog model. Supporting, LOE 5, Quality Poor


5. Brunn GJ, Keyler DE, Ross CA, Pond SM, Pentel PR. Drug-specific F(ab’)2 fragment reduces desipramine cardiotoxicity in rats. *Int J Immunopharmacol*. 1991;13:841-851. **Reviewer Summary:** A small, controlled animal study of the effects of desipramine Fab on desipramine induced cardiotoxicity. Fab significantly reduced QRS prolongation, increased total and reduced free serum desipramine levels. **Reviewer Conclusion:** This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study. A saline control group would have added to the quality of the study. Supporting, LOE 5, Quality Poor
6. Brunn GJ, Keyler DE, Pond SM, Pentel PR. Reversal of desipramine toxicity in rats using drug-specific antibody Fab' fragment: effects on hypotension and interaction with sodium bicarbonate. *J Pharmacol Exp Ther.* 1992;260:1392-1399. **Reviewer Summary:** A small, controlled animal study assessing the efficacy of 1) anti tricyclic Fab for desipramine induced hypotension and 2) tricyclic Fab and/or sodium bicarbonate for desipramine induced QRS prolongation. The tricyclic Fab group demonstrated significant improvements in mean arterial pressure compared to control. Both the tricyclic Fab group and the sodium bicarbonate group demonstrated improvements in QRS duration, and the combination of tricyclic Fab + sodium bicarbonate was superior to either agent alone. **Reviewer Conclusion:** This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study. **Supporting, LOE 5, Quality Good.**

7. Callaham M, Schumaker H, Pentel P. Phenytoin prophylaxis of cardiotoxicity in experimental amitriptyline poisoning. *J Pharmacol Exp Ther.* 1988;245:216-220. **Reviewer Summary:** Experimental dog study of the effects of phenytoin pretreatment on amitriptyline toxicity in comparison to control. The phenytoin group developed toxicity, defined as QRS widening greater than 50%, at a higher dose of amitriptyline than control. The onset of first ventricular tachycardia was the same between groups, but the summed duration and frequency of ventricular tachycardia was greater in the phenytoin group. The total dose of amitriptyline at death was the same between groups, though time to death is not specified. **Reviewer Conclusion:** The study fails to demonstrate a beneficial effect of phenytoin pretreatment in a dog model of amitriptyline toxicity. **Neutral, LOE 5, Quality Good.**

8. Dart R, Sidki A, Sullivan JB, Egen NB, Garcia RA. Ovine desipramine antibody fragments reverse desipramine cardiovascular toxicity in the rat. *Annals of Emergency Medicine.* 1996;27:309-315. **Reviewer Summary:** A small, controlled animal study of Fab fragments for desipramine toxicity, with escalating doses of Fab. The study demonstrated efficacy of fab fragments in reducing toxicity with a dose response. **Reviewer Conclusion:** This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study. **Supporting, LOE 5, Quality Good.**

9. Follmer CH, Lum BK. Protective action of diazepam and of sympathomimetic amines against amitryptyline-induced toxicity. *J Pharmacol Exp Ther.* 1982;222:424-429. **Reviewer Summary:** Experimental cat study of the effects of mechanical ventilation, sympathomimetic amines, and diazepam on amitriptyline toxicity in comparison to control. Mechanical ventilation and diazepam studies were pre-treatment models, and the sympathomimetic study was co-infusion of amitriptyline and intervention. The study demonstrated a beneficial effect of mechanical ventilation (increased time to death), diazepam (abolished seizures, less mortality), dobutamine and dopamine infusion (less bradycardia, less myocardial depression, less AV block). Isoproterenol had a more modest beneficial effect on the chronotropic and inotropic effects but only at the lower dose studied. **Reviewer Conclusion:** The study indicates a beneficial effect of mechanical ventilation, diazepam, and sympathomimetic agents, specifically dopamine and dobutamine, in a cat model of amitriptyline toxicity. **Supporting, LOE 5, Quality Good.**

10. Hagerman GA, Hanashiro PK. Reversal of tricyclic-antidepressant-induced cardiac conduction abnormalities by phentoin. *Annals of Emergency Medicine.* 1981;10:82-86. **Reviewer Summary:** Case series of 10 patients who received intravenous phentoin for treatment of presumed amitriptyline induced cardiac conduction abnormalities. The paper presents limited data about the pre-phentoin condition of the patients other receiving supportive care until they were clinically stable. Interventions such as intubation, vasopressors, and sodium bicarbonate are not specified. 9 patients are described as having a prolonged PR interval, though only one has a PR interval >200ms. Only 5 of the 10 patients have a QRS duration >120. Documentation of the timeline of resolution of conduction abnormalities is insufficient as is the effect on hemodynamics and mental status. **Reviewer Conclusion:** The study indicates that phentoin may improve cardiac conduction abnormalities due to tricyclic overdose in clinically stable patients. It is unclear from this study if the effect translates into improved patient outcome. **Supporting, LOE 4, Quality Poor.**

11. Harvey M, Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. *Annals of Emergency Medicine.* 2007;49:178-85, 185.e1-4. **Reviewer Summary:** Randomized, controlled, unblinded study of sodium bicarbonate versus intralipid in a rabbit model of clomipramine toxicity. The main beneficial outcome was more rapid and complete resolution of hypotension and aversion of cardiovascular collapse in the intralipid groups. Outside of the limitations inherent to animal studies in
general, the intralipid groups in this study received four fold more volume during the rescue intervention than the bicarbonate groups. Given that resolution of hypotension was the main finding, this is a major criticism. **Reviewer Conclusion:** The study demonstrated that intralipid infusion ameliorates hypotension and cardiovascular collapse in a rabbit model of clomipramine toxicity. Direct comparison to sodium bicarbonate is limited in this experimental model. Supporting, LOE 5, Quality Poor

12. Heard K, Dart RC, Bogdan G, O'Malley GF, Burkhart KK, Donovan JW, Ward SB. A preliminary study of tricyclic antidepressant (TCA) ovine FAB for TCA toxicity. **LCLT.** 2006;44:275-281. **Reviewer Summary:** A small, uncontrolled human study of ovine derived tricyclic Fab for tricyclic toxicity. The primary outcome measure was pharmacokinetic changes post administration. Patients demonstrated increases in total tricyclic serum concentrations, the free proportion fell, there was no increase in tricyclic toxicity, and adverse reactions were minimal. However, clinical advantages for this therapy remain undetermined. **Reviewer Conclusion:** Ovine derived tricyclic Fab was administered safely in this small group of mildly to moderately poisoned patients and is worthy of further study. Supporting, LOE 4, Poor

13. Hedges JR, Baker PB, Tasset JI, Otten EJ, Dalsey WC, Syverud SA. Bicarbonate therapy for the cardiovascular toxicity of amitriptyline in an animal model. **J Emerg Med.** 1985;3:253-260. **Reviewer Summary:** Experimental dog study assessing the effect of sodium bicarbonate following induction of amitriptyline toxicity. Critiques include two of the seven experimental animals did not survive to receive the intervention and that the animals served as their own controls. **Reviewer Conclusion:** The study demonstrated that sodium bicarbonate is effective in reducing QRS duration, dysrhythmias, and hypotension in a dog model. Supporting, LOE 5, Quality Poor

14. Hoffman JR, Votey SR, Bayer M, Silver L. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe cyclic antidepressant overdose. **The American Journal of Emergency Medicine.** 1993;11:336-341. **Reviewer Summary:** Retrospective review of 91 patients diagnosed with cyclic antidepressant overdose who received sodium bicarbonate treatment in the emergency department. The study documented improvements in blood pressure, QRS duration, and mental status following sodium bicarbonate therapy. No adverse effects of sodium bicarbonate were detected. **Reviewer Conclusion:** The study provides evidence that sodium bicarbonate is a safe and effective therapy for cyclic antidepressant toxicity. However, the limitations of retrospective chart reviews and lack of controls must be considered. Supporting, LOE 4, Quality Good

15. Hursting MJ, Opheim KE, Raisys VA, Kenny MA, Metzger G. Tricyclic antidepressant-specific Fab fragments alter the distribution and elimination of desipramine in the rabbit: a model for overdose treatment. **J Toxicol Clin Toxicol.** 1989;27:53-66. **Reviewer Summary:** A small animal study assessing the ability of sheep derived Fab fragments to alter the distribution and elimination of desipramine in a favorable manner. Following Fab administration the total and bound serum concentration of desipramine increased, which is consistent with a decrease in the amount available to bind to relevant receptor sites, and was followed by increased urinary clearance. **Reviewer Conclusion:** This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study. Supporting, LOE 5, Quality Poor

16. Johnson PB. Phystostigmine in tricyclic antidepressant overdose. **JACEP.** 1976;5:443-445. **Reviewer Summary:** A short case series of patients treated with phystostigmine for presumed amitriptyline toxicity. The report fails to include confirmatory data for the ingestant(s), lacks EKG data, and has an insufficient follow-up duration. **Reviewer Conclusion:** The paper indicates that phystostigmine transiently reversed the anticholinergic effects of the four cases reported but fails to document the safety of the intervention, and is inadequate to make conclusions about a treatment recommendation. Supporting, LOE 4, Quality Poor

17. Kline JA, DeStefano AA, Schroeder JD, Raymond RM. Magnesium potentiates imipramine toxicity in the isolated rat heart. **Annals of Emergency Medicine.** 1994;24:224-232. **Reviewer Summary:** Experimental isolated rat heart (Langendorf preparation) model to assess the effects of magnesium or hypertonic alkaline solution in the setting of imipramine toxicity. Magnesium worsened mechanical function and conduction. Hypertonic alkaline solution reduced conduction defects. **Reviewer Conclusion:** The study demonstrates that magnesium is deleterious in an isolated rat heart model of imipramine toxicity. However, this model fails to account for the neurohormonal and circulatory abnormalities that occur in an intact animal model. Opposing, LOE 5, Quality Fair

effects of epinephrine and norepinephrine, or placebo in an experimental model of amitriptyline toxicity. Epinephrine and norepinephrine improved mean arterial pressure, heart rate and dP/dT. Malignant arrhythmias were not more common in treated animals than controls, however they were more common in the norepinephrine group than the epinephrine group. There was a mortality benefit for both vasopressors and was greatest for epinephrine. **Reviewer Conclusion:** The study demonstrated improved cardiac performance and reduced mortality for epinephrine>norepinephrine>control, without increased risk of arrhythmia or hypotension, in a rat model of amitriptyline toxicity. Supporting, LOE 5, Quality Fair

19. 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. *Critical Care Medicine.* 1994;22:1851-1855. **Reviewer Summary:** Non-randomized, controlled rat study of the effects of epinephrine, norepinephrine, magnesium sulfate, and milrinone on survival and the occurrence of amitriptyline toxicity. All study drugs increased survival without increasing the risk of arrhythmias. Epinephrine, epinephrine plus magnesium sulfate, and norepinephrine plus magnesium sulfate were effective in preventing arrhythmias. **Reviewer Conclusion:** The study demonstrates that a range of vasopressors increase survival, and that magnesium may have an added antiarrhythmic effect when used in combination with epinephrine and norepinephrine in this rat model of amitriptyline toxicity. Supporting, LOE 5, Quality Fair

20. Knudsen K, Abrahamsson J. Effects of magnesium sulfate and lidocaine in the treatment of ventricular arrhythmias in experimental amitriptyline poisoning in the rat. *Crit Care Med.* 1994;22:494-498. **Reviewer Summary:** Non-randomized, controlled rat study of the effects of lidocaine vs magnesium on norepinephrine/amitriptyline induced ventricular tachycardia. 90% of rats treated with magnesium sulfate converted to sinus rhythm as compared to 10% in the lidocaine and control group. The magnesium sulfate group also suffered more hypotension and bradycardia. **Reviewer Conclusion:** The study demonstrates that magnesium sulfate is effective in restoring sinus rhythm in a rat model of hyperadrenergic amitriptyline induced ventricular tachycardia, with the disadvantage of inducing bradycardia and hypotension. Neutral, LOE 5, Quality Fair

21. Knudsen K, Abrahamsson J. Epinephrine and sodium bicarbonate independently and additively increase survival in experimental amitriptyline poisoning. *Crit Care Med.* 1997;25:669-674. **Reviewer Summary:** Non-randomized, controlled rat study of the effects of epinephrine, norepinephrine, sodium bicarbonate, epinephrine plus sodium bicarbonate, norepinephrine plus sodium bicarbonate, or placebo in an experimental model of amitriptyline toxicity. The study demonstrated that, in terms of survival, epinephrine, norepinephrine, and sodium bicarbonate independently increased survival, there was an additive beneficial effect of sodium bicarbonate to vasopressor infusion, and epinephrine infusion plus sodium bicarbonate was the most efficacious therapy. Rats receiving sodium bicarbonate had the longest time to onset of arrhythmia, those receiving epinephrine plus sodium bicarbonate had the greatest cumulative time in sinus rhythm. **Reviewer Conclusion:** The study demonstrates that epinephrine was the vasopressor of choice in this rat model of amitriptyline toxicity, and that sodium bicarbonate has an independent and additive effect. Supporting, LOE 5, Quality Fair

22. Köppel C, Wiegreffe A, Tenczer J. Clinical course, therapy, outcome and analytical data in amitriptyline and combined amitriptyline/chlordiazepoxide overdose. *Human & experimental toxicology.* 1992;11:458-465. **Reviewer Summary:** Case series of 184 patients with amitriptyline overdose or combined chlordiazepoxide/amitriptyline overdose. Hypertonic sodium bicarbonate was effective in reducing the QRS duration in 4/8 patients with conduction disturbances. Physostigmine reversed anticholinergic effects in 8/14 patients. Hemoperfusion improved coma in 4/5 patients. **Reviewer Conclusion:** The paper supports the use of sodium bicarbonate in patients with conduction abnormalities. Physostigmine and hemoperfusion are more controversial therapies and the paper does not support use at this time. Supporting, LOE 4, Quality Fair

23. Levitt MA, Sullivan JB, Owens SM, Burnham L, Finley PR. Amitriptyline plasma protein binding: effect of plasma pH and relevance to clinical overdose. *Am J Emerg Med.* 1986;4:121-125. **Reviewer Summary:** In vitro study of the effects of pH on the free fraction vs protein bound fraction of amitriptyline. **Reviewer Conclusion:** The study demonstrated significant reductions in the free fraction of amitriptyline as pH increased from 7.11 to 7.83, and supports the concept of alkalization in amitriptyline toxicity. Supporting, LOE 5, Quality Fair

toxicity. Ventilation, blood pressure, and pH were not monitored and the animals served as their own controls. **Reviewer Conclusion:** The study demonstrated no beneficial effect of prophylactic phenytoin on development of cardiac conduction abnormalities or dose to death, and there was minimal effect on conduction abnormalities in an uncontrolled group subjected to rescue therapy with phenytoin. Neutral, LOE 5, Quality Poor

25. McCabe JL, Menegazzi JJ, Cobaugh DJ, Auble TE. Recovery from severe cyclic antidepressant overdose with hypertonic saline/dextran in a swine model. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* 1994;1:111-115. **Reviewer Summary:** Randomized, controlled swine study of the effect of hypertonic saline and dextran solution versus saline control on nortriptyline toxicity. **Reviewer Conclusion:** The study demonstrated that a 10mL/kg 7.5% saline/6% dextran infusion significantly reversed hypotension, QRS prolongation, and survival to 60 minutes in comparison to the same volume of normal saline. A study comparing this intervention to the standard of care, sodium bicarbonate, is required. Supporting. LOE 5, Quality Good

26. McCabe JL, Cobaugh DJ, Menegazzi JJ, Fata J. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Annals of Emergency Medicine.* 1998;32:329-333. **Reviewer Summary:** Randomized, controlled swine model of hypertonic saline, sodium bicarbonate, and hyperventilation versus control in an experimental model of nortriptyline toxicity. Hypertonic saline was effective in reversing ventricular tachycardia, decreasing QRS duration, improving blood pressure, and improving survival as compared to control. Sodium bicarbonate was effective in reversing ventricular tachycardia, but was less effective in decreasing QRS duration, improving blood pressure, and in survival benefit. Hyperventilation did appear to decrease QRS duration modestly. The main critique is that the sodium bicarbonate group was infused with 3 mEq/kg (3cc/kg) 8.4% sodium bicarbonate followed by 7cc/kg isotonic D5W; the hyperventilation group received 10cc/kg D5W. This is a significant confounding variable. **Reviewer Conclusion:** The study demonstrated that hypertonic saline is efficacious in reversing nortriptyline induced cardiotoxicity in a swine model, comparison to sodium bicarbonate and hyperventilation is limited by confounding variables. Supporting. LOE 5, Quality Poor

27. Nattel S, Keable H, Sasyniuk BI. Experimental amitriptyline intoxication: electrophysiologic manifestations and management. *J Cardiovasc Pharmacol.* 1984;6:83-89. **Reviewer Summary:** Non-randomized, uncontrolled dog experimental study on the cardiac effects of amitriptyline infusion, followed by observation of the effects of sodium bicarbonate infusion. Amitriptyline significantly increased heart rate, QRS duration, and AH and HV intervals. Ventricular tachyarrhythmias occurred following marked QRS widening. Sodium bicarbonate was noted to rapidly reverse the arrhythmias. **Reviewer Conclusion:** The study supports the use of sodium bicarbonate in the setting of amitriptyline cardiotoxicity. Supporting. LOE 5, Quality Poor

28. Nattel S, Mittleman M. Treatment of ventricular tachyarrhythmias resulting from amitriptyline toxicity in dogs. *J Pharmacol Exp Ther.* 1984;231:430-435. **Reviewer Summary:** Randomized, controlled, blinded experimental dog study of the effects of lidocaine and sodium bicarbonate in comparison to saline control in amitriptyline induced cardiotoxicity. The effect of hyperventilation was also studied in an unblinded, non-randomized manner. Sodium bicarbonate 2mEq/kg significantly reduced arrhythmia frequency and duration, reduced QRS duration, and maintained blood pressure. The effect of lidocaine was less pronounced and of shorter duration, in addition it was associated with decreases in blood pressure and did not effect QRS prolongation. Hyperventilation showed a delayed effect on resolving arrhythmias and decreased QRS and QT intervals. Hypertonic saline (2mEq/kg) effects were highly variable and not statistically significant. **Reviewer Conclusion:** The study supports the use of sodium bicarbonate in the setting of amitriptyline induced cardiotoxicity and suggests that hyperventilation may be beneficial. Supporting. LOE 5, Quality Good

29. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA.* 1975;231:941-943. **Reviewer Summary:** Case series of 21 patients with tricyclic antidepressant overdose. Of the 11 patients presenting in an unconscious state, all regained consciousness following physostigmine injection, and sinus tachycardia resolved when present. In this group two patients had seizures, one experienced hypersalivation, and one had hypotension following physostigmine. Tricyclic induced symptoms recurred in all patients within 30 minutes. Of the 10 patients that were conscious but agitated, agitation resolved in all following physostigmine, and there were no reported complications. Recurrence of symptoms was not reported in this group. No patient in either group was reported to have QRS prolongation prior to physostigmine. Adverse reactions in the setting of sodium channel blockade cannot be commented on.
Reviewer Conclusion: The high rate of adverse reactions and transient nature of the therapeutic effect demonstrated in this small case series indicates that physostigmine cannot be recommended as a standard intervention for symptomatic tricyclic overdose patients.

Supporting, LOE 4, Quality Fair

30. Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. Annals of Emergency Medicine. 1980;9:588-590. Reviewer Summary: A case series of two patients who developed asystole following physostigmine administered for seizure activity following large ingestions of tricyclic antidepressants. Following arrest, they received chest compressions, epinephrine, and sodium bicarbonate, to which they responded. Reviewer Conclusion: The two cases suggest that physostigmine may have detrimental effects when used as therapy for symptomatic tricyclic ingestions. It also suggests that epinephrine and sodium bicarbonate may be beneficial in tricyclic antidepressant induced cardiac arrest. However, the fact that physostigmine was administered immediately pre-arrest significantly limits the strength of this conclusion. For physostigmine: Opposing, LOE 4, Quality Poor; For epinephrine and sodium bicarbonate: Supporting, LOE, Quality Poor.

31. Pentel P, Benowitz N. Efficacy and mechanism of action of sodium bicarbonate in the treatment of desipramine toxicity in rats. J Pharmacol Exp Ther. 1984;230:12-19. Reviewer Summary: Non-randomized, unblinded, controlled rat study on the effects of two concentrations of sodium bicarbonate, two concentrations of hypertonic saline, two concentrations of sodium bicarbonate and potassium chloride, and respiratory acidosis and alkalosis in an experimental model of desipramine toxicity. Sodium bicarbonate, hypertonic saline, and sodium bicarbonate/potassium chloride reduced the amitriptyline induced QRS prolongation in a dose dependent manner and had similar beneficial effects on blood pressure. Respiratory acidosis exacerbated the desipramine induced QRS prolongation. Reviewer Conclusion: The study supports the current use of hypertonic sodium bicarbonate in treatment of tricyclic cardiotoxicity. It also demonstrates efficacy of hypertonic saline, and indicates that respiratory acidosis is deleterious in rat models of tricyclic cardiotoxicity.

Supporting, LOE 5, Quality Poor

32. Pentel PR, Ross CA, Landon J, Sidki A, Shelver WL, Keyler DE. Reversal of desipramine toxicity in rats with polyclonal drug-specific antibody Fab fragments. J Lab Clin Med. 1994;123:387-393. Reviewer Summary: A small randomized, controlled rat study on the efficacy of polyclonal ovine Fab against common tricyclic antidepressant drugs. The groups of rats that received the polyclonal Fab demonstrated improved QRS duration, with a positive although less pronounced effect on blood pressure. The study would have benefited from post-hoc analysis on data where repeated measures ANOVA detected a significant interaction. Reviewer Conclusion: This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study.

Supporting, LOE 5, Quality Fair

33. Pentel PR, Scarlett W, Ross CA, Landon J, Sidki A, Keyler DE. Reduction of desipramine cardiotoxicity and prolongation of survival in rats with the use of polyclonal drug-specific antibody Fab fragments. Annals of Emergency Medicine. 1995;26:334-341. Reviewer Summary: A small animal study on the effects of ovine derived fab fragments for desipramine toxicity, focusing on ability to prolong survival, alter pharmacokinetics, and to assess for interactions with sodium bicarbonate. In general, Fab use improved survival, hemodynamics, and ekg findings. Reviewer Conclusion: This small animal study demonstrates that the concept of Fab antidotal therapy for tricyclic toxicity is feasible and worthy of further study.

Supporting, LOE 5, Quality Poor

34. Sangster B, de Groot G, Borst C, de Wildt D. Dopamine and isoproterenol in imipramine intoxication in the dog. J Toxicol Clin Toxicol. 1985;23:407-420. Reviewer Summary: An unblinded, non-randomized, controlled dog experiment on the efficacy of dopamine and isoproterenol to treat imipramine cardiotoxicity. The dopamine and isoproterenol groups demonstrated longer time to death, higher tolerated imipramine dose, and improved hemodynamics (dopamine: high pressure/low output; isoproterenol: low pressure/high output). Reviewer Conclusion: The paper provides experimental support for the use of dopamine and isoproterenol in a dog model of imipramine cardiotoxicity, the ideal agent or combination of agents in humans requires further study.

Supporting, LOE 5, Quality Fair

35. Sasyniuk BI, Jhamandas V. Mechanism of reversal of toxic effects of amitriptyline on cardiac Purkinje fibers by sodium bicarbonate. J Pharmacol Exp Ther. 1984;231:387-394. Reviewer Summary: In vitro study of amitriptyline poisoned dog purkinje fibers and the effect of sodium bicarbonate. Reviewer Conclusion: The study demonstrates sodium bicarbonate improves amitriptyline induced abnormalities in action potential amplitude and V_max particularly for phase 0, and suggests that this is due to both alkalinization and increased
extracellular sodium concentration. Supporting, LOE 5, Quality Fair

36. Sasyniuk BI, Jhamandas V, Valois M. Experimental amitriptyline intoxication: treatment of cardiac toxicity with sodium bicarbonate. Annals of Emergency Medicine. 1986;15:1052-1059. **Reviewer Summary:** Non-randomized, uncontrolled, unblinded dog study of the effect of sodium bicarbonate on experimentally induced amitriptyline toxicity. An in vitro component was also performed. **Reviewer Conclusion:** The study supports the current standard of using sodium bicarbonate for tricyclic induced cardiotoxicity. Supporting, LOE 5, Quality Fair

37. Stone CK, Kraemer CM, Carroll R, Low R. Does a sodium-free buffer affect QRS width in experimental amitriptyline overdose? Ann Emerg Med. 1995;26:58-64. **Reviewer Summary:** Prospective, uncontrolled, unblinded experimental dog study of the effects of pH manipulation, without sodium loading, on amitriptyline cardiotoxicity. The main limitation is the lack of a control group to assess efficacy in comparison to sodium bicarbonate. **Reviewer Conclusion:** The study demonstrated a correlation between increased pH, induced by intravenous tromethamine, and decreased QRS width. Supporting, LOE 5, Quality Poor

38. Teba L, Schiebel F, Dedhia HV, Lazzell VA. Beneficial effect of norepinephrine in the treatment of circulatory shock caused by tricyclic antidepressant overdose. The American Journal of Emergency Medicine. 1988;6:566-568. **Reviewer Summary:** A two patient case series of patients with severe tricyclic induced cardio and neurotoxicity unresponsive to standard measures including dopamine as a vasopressor. Following a change in vasopressor to norepinephrine blood pressure normalized. **Reviewer Conclusion:** The case series suggests that norepinephrine is a reasonable choice for a vasopressor in tricyclic induced cardiotoxicity. Supporting, LOE 4, Quality Poor

39. Tobis J, Aronow WS. Effect of amitriptyline antidotes on repetitive extrasystole threshold. Clin Pharmacol Ther. 1980;27:602-606. **Reviewer Summary:** Experimental study of the effects of physostigmine, propranolol, sodium bicarbonate, and left stellate ganglionectomy on the repetitive extrasystole threshold (the current required to induce at least one depolarization after premature electrical input) in amitriptyline poisoned dogs. All interventions increased the repetitive extrasystole threshold, however the effect of sodium bicarbonate was not significant. **Reviewer Conclusion:** The paper provides useful information pertaining to the mechanism of amitryptiline toxicity, including the potential of a centrally mediated effect. It does not provide guidance as to the clinical management of tricyclic poisoned patients. Neutral, LOE 5, Quality Fair

40. Tran TP, Panacek EA, Rhee KJ, Foulke GE. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. Acad Emerg Med. 1997;4:864-868. **Reviewer Summary:** Retrospective cohort study of patients receiving vasopressors for hypotension suspected to be induced by tricyclic overdose, comparing norepinephrine to dopamine. Inclusion criteria were lax, and treatment was not standardized resulting in the potential for multiple confounders. 11/11 patients started on norepinephrine for refractory hypotension responded; 9/15 started on dopamine responded. The 6 patients who failed dopamine responded to subsequent norepinephrine infusions. One patient in the norepinephrine group developed ventricular ectopy which responded to lidocaine therapy. **Reviewer Conclusion:** The study indicates that norepinephrine may be the vasopressor of choice for tricyclic induced hypotension. Supporting, LOE 3, Quality Poor

41. Vernon DD, Jr BW, Garrett JS, Dean JM. Efficacy of dopamine and norepinephrine for treatment of hemodynamic compromise in amitriptyline intoxication. Crit Care Med. 1991;19:544-549. **Reviewer Summary:** Experimental, dog study comparing the efficacy of various infusion rates of dopamine and norepinephrine on amitriptyline induced hemodynamic abnormalities. The dogs served as their own controls. Norepinephrine at 0.25, 0.5, and 1.0 mcg/kg/min and dopamine at 15 and 30 mcg/kg/min but not 5 mcg/kg/min improved hemodynamic variables (cardiac output, peak left ventricular dP/dT, and mean arterial pressure). Hemodynamic variables at the highest doses were not different. **Reviewer Conclusion:** The study indicates that both dopamine and norepinephrine are effective in treating amitriptyline induced hemodynamic alterations. Supporting, LOE 5, Quality Fair

42. Yoav G, Odelia G, Shaltiel C, Goor Y, Goor O, Cabili S. A lipid emulsion reduces mortality from clomipramine overdose in rats. Veterinary and human toxicology. 2002;44:30. (abstract only) **Reviewer Summary:** Experimental rat study of the effect of an intralipid vehicle for administration of clomipramine versus normal saline vehicle. The rats receiving clomipramine in an intralipid vehicle demonstrated lower mortality. **Reviewer Conclusion:** This study provides further justification for the study of intralipid as an antidote to neurotoxic and cardiotoxic drugs. Supporting, LOE 5, Quality Fair