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REVIEW

Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning*

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ABSTRACT

Background: Although intravenous lipid emulsion (ILE) was first used to treat life-threatening local anesthetic (LA) toxicity, its use has expanded to include both non-local anesthetic (non-LA) poisoning and less severe manifestations of toxicity. A collaborative workgroup appraised the literature and provides evidence-based recommendations for the use of ILE in poisoning.

Methods: Following a systematic review of the literature, data were summarized in four publications: LA and non-LA poisoning efficacy, adverse effects, and analytical interferences. Twenty-two toxins or toxin categories and three clinical situations were selected for voting. Voting statements were proposed using a predetermined format. A two-round modified Delphi method was used to reach consensus on the voting statements. Disagreement was quantified using RAND/UCLA Appropriateness Method.

Results: For the management of cardiac arrest, we recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins. For the management of life-threatening toxicity, (1) as first line therapy, we suggest not to use ILE with toxicity from amitriptyline, non-lipid soluble beta receptor antagonists, bupropion, calcium channel blockers, cocaine, diphenhydramine, lamotrigine, malathion but are neutral for other toxins, (2) as part of treatment modalities, we suggest using ILE in bupivacaine toxicity if other therapies fail, but are neutral for other toxins, (3) if other therapies fail, we recommend ILE for bupivacaine toxicity and we suggest using ILE for toxicity due to other LAs, amitriptyline, and bupropion, but our recommendations are neutral for all other toxins. In the treatment of non-life-threatening toxicity, recommendations are variable according to the balance of expected risks and benefits for each toxin.

For LA-toxicity we suggest the use of Intralipid[®] 20% as it is the formulation the most often reported. There is no evidence to support a recommendation for the best formulation of ILE for non-LAs. The voting panel is neutral regarding ILE dosing and infusion duration due to insufficient data for non-LAs. All recommendations were based on very low quality of evidence.

Conclusion: Clinical recommendations regarding the use of ILE in poisoning were only possible in a small number of scenarios and were based mainly on very low quality of evidence, balance of expected risks and benefits, adverse effects, laboratory interferences as well as related costs and resources. The workgroup emphasizes that dose-finding and controlled studies reflecting human poisoning scenarios are required to advance knowledge of limitations, indications, adverse effects, effectiveness, and best regimen for ILE treatment.

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Fat emulsion; lipid resuscitation; recommendation; adverse effect; lipid interference

Introduction

The lipid emulsion workgroup was established as a collaborative effort among the American Academy of Clinical Toxicology, the European Association of Poison Centres and Clinical Toxicologists, the American College of Medical Toxicology, the Asia Pacific Association of Medical Toxicology, the American Association of Poison Control Centers, and the Canadian Association of Poison Control Centers. This article presents the workgroup's recommendations regarding the use of intravenous lipid emulsion therapy in poisoning for a preselected set of toxins. These recommendations are based on the results of four systematic reviews,^[1–4] derived from a comprehensive analysis of the published evidence and further followed by an expert consensus.

Methods

The detailed methodology for the workgroup's process was previously published.^[5] Each association selected clinical experts to serve on this committee and additional selections were made for their specific expertise in related fields. Two medical librarians assisted the workgroup in the design of the search strategies, article retrieval, and management of citations but did not vote on the recommendations. For the published systematic reviews, the following databases were searched from inception to 15 December 2014: BIOSIS Previews (via Ovid), CINAHL (via EBSCO), the Cochrane Library/DARE, Embase (via Ovid), Medline (Ovid), PubMed, Scopus, and Web of Science. The literature review was updated in December 2015 as described later. No language restrictions were applied. Articles in languages other than English were professionally translated. A methodologist with expertise in systematic reviews and guideline development oversaw the process. The workgroup considered four systematic reviews that summarized the evidence pertaining to potential benefits and harms of the use of lipid emulsion in poisoning, which were published prior to finalizing the recommendations, and an international survey evaluating ILE availability and cost.^[1–4,6]

The voting panel decided to evaluate only those toxins or categories of toxins for which a minimum of three human cases were reported in the literature. The 22 toxins or categories were selected as the following: amitriptyline, class 1 antidysrhythmics, baclofen, bupivacaine, bupropion, lipid-soluble beta-receptor antagonists (defined as a positive log *D*), non-lipid-soluble beta-receptor antagonists, cocaine, non-dihydropyridine calcium channel blockers (diltiazem and verapamil), dihydropyridine calcium channel blockers, diphenhydramine, ivermectin, lamotrigine, malathion, olanzapine, selective serotonin receptor inhibitors, other cyclic antidepressants, other antihistamines, other antipsychotics, other insecticides, other local anesthetics (LAs), and other pesticides.

The workgroup determined clinical situations in which lipid emulsion could be indicated. These were categorized as (1) cardiac arrest, (2) life-threatening toxicity, or (3) non-life-threatening toxicity (Table 1). Life-threatening toxicity was

Table 1. Intravenous lipid emulsion (ILE) in poisoning: clinical situations.

Statements	Clinical situations
ILE is indicated in cardiac arrest, after standard ACLS is started	
ILE is indicated in life-threatening toxicity	As first-line therapy As part of treatment modalities If other therapies fail (in last resort)
ILE is indicated in non-life-threatening toxicity	As first-line therapy As part of treatment modalities If other therapies fail (in last resort)

defined as the presence of any of the following: dysrhythmias such as ventricular tachycardia with compromised organ perfusion, ventricular fibrillation, status epilepticus, and/or hypotension with organ compromise. Shock or end-organ compromise was defined as the presence of cellular ischemia as evidenced by increased lactate concentration, acute kidney injury as defined by the Kidney Disease Improving Global Outcomes (KDIGO) guideline,^[7] increased troponin, altered mental status, or decreased capillary refill. Hypotension was defined as a low blood pressure as per age-related defined standards. Non-life-threatening toxicity was defined as clinical situations without immediate threat to life such as coma, altered mental status, simple seizure, hypotension without organ compromise, and dysrhythmias such as sinus tachycardia or other stable dysrhythmias. Altered mental status was defined as the impairment in one of the spheres of brain function: cognition, alertness or orientation, and coma a deep state of unconsciousness as per the American Academy of Neurology.^[8]

A generic format of voting statements was developed during several conference calls in order to refine the final wording and ensure generalizability to all toxins (Appendix 1). A two-round modified Delphi method was utilized to reach a consensus on clinical recommendations. After considering the balance between desirable and undesirable outcomes, the quality of evidence for outcomes as well as costs and resource use, members of the voting panel cast their votes on a 9-point Likert scale for each proposed statement for each toxin/category of toxins included. The RAND/UCLA Appropriateness Method was used to quantify disagreement between the votes cast by the panel. The median values, the lower/upper quartiles, and the disagreement indexes were calculated for each of the two rounds of votes. Median values ranging from 7 to 9 reflected that the workgroup was in favor of the proposed statement, 4 to 6 reflected a neutral position, and 1 to 3 reflected that the workgroup was against the statement. The disagreement index describes the dispersion of ratings and values less than or equal to 1 indicate agreement. A second round of voting determined the final strength of recommendations (Figure 1). A strong recommendation in favor (level 1) was defined as a median value between 7 and 9 with a lower quartile between 7 and 9 and a disagreement index ≤ 1 (similarly, a strong recommendation against was defined as a median value between 1 and 3 with an upper quartile between 1 and 3 and a disagreement index ≤ 1). A weak/conditional recommendation in favor (level 2) was defined as a median value between 7 and 9 with a lower quartile between 4 and 6 and a disagreement

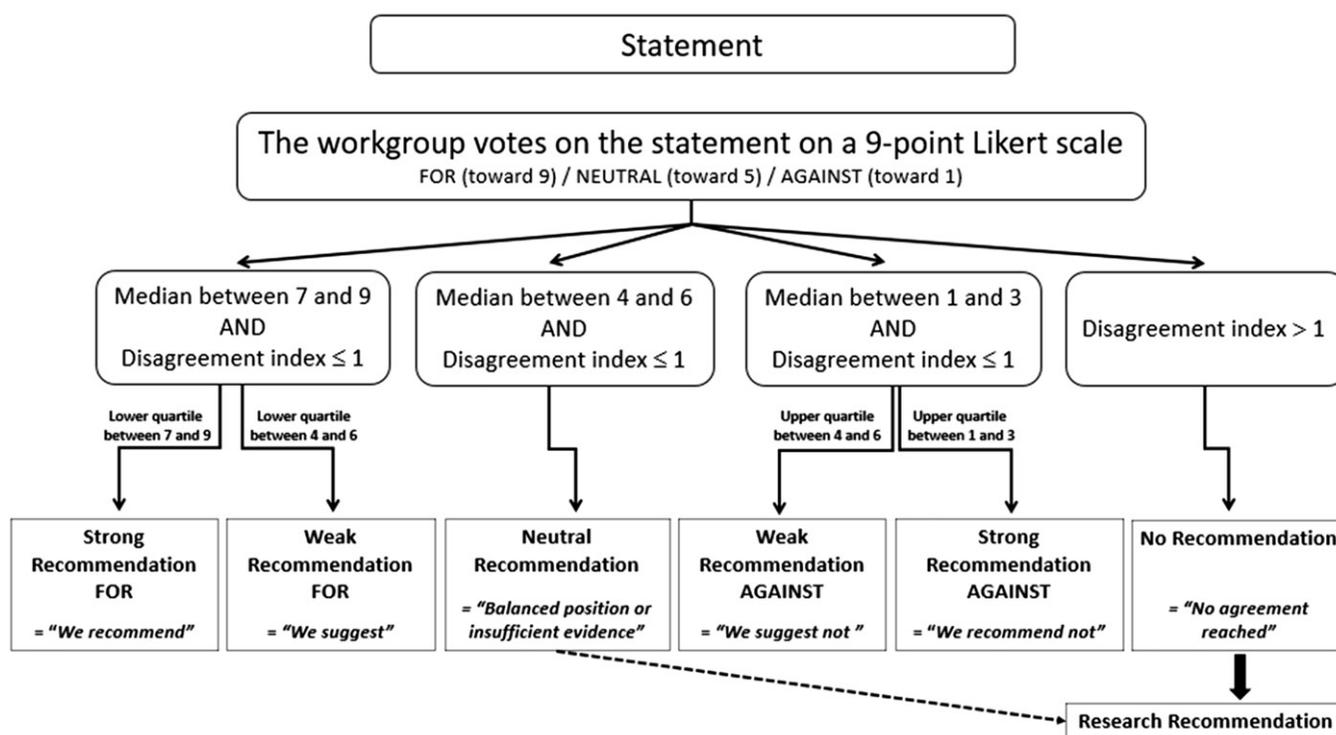


Figure 1. Voting process.

index ≤ 1 (similarly, a weak/conditional recommendation against was defined as a median value between 1 and 3 with an upper quartile between 4 and 6 and a disagreement index ≤ 1). A neutral position was resulted when the median value was between 4 and 6 with a disagreement index ≤ 1 . To better understand the reason for a neutral vote, members could specify if their position was neutral due to major uncertainties in the evidence or to a balance between the desirable and undesirable effects of adherence to the proposed statement. When the disagreement index exceeded 1, no recommendation resulted as this illustrated an inability of the voting panel to reach consensus. All recommendations are followed by the strength of recommendations (1 or 2) and the grading of the level of evidence (A to D) (Table 2), in accordance with the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation).[9]

A first vote occurred in October 2014 and results were discussed in a face-to-face meeting in the same month. A second vote in September 2015 determined the final recommendations. Results were discussed in a second face-to-face meeting in October 2015. An update of the literature for publications through 31 December 2015 was performed in January 2016 using the same search strategy previously mentioned and is presented in Appendices 2–4. The literature update was summarized and presented to the members of the voting panel. Members were given an opportunity to update their votes in March of 2016.

Clinical recommendations

In the discussions that follow if there is no specific mention of a scenario, it is implied that the voting was neutral.

The complete voting results for each statement for each toxin/category of toxins are presented in Appendix 5. An executive summary of the recommendations for all toxins/categories of toxins is presented in Table 3.

Recommendations for local anesthetics

Indications:

- In cardiac arrest due to toxicity of bupivacaine, we recommend using ILE after standard ACLS is started (1D), while our recommendation is neutral regarding its use in cardiac arrest due to other local anesthetics.

Rationale: The voting panel noted that bupivacaine is the LA for which the most data exist with results supporting the efficacy of ILE. However, controlled data from animal experiments suffer from several methodological shortcomings. These include: reporting a statistical difference for short experimental time frames not directly relevant to clinical situations, the failure to perform autopsies to search for potential adverse effects, and the lack of reporting of acidosis and hypoxia in study animals, both of which are common in human poisonings and can affect outcome. Human case reports are too heterogeneous and patients received concurrent multiple other medications making it impossible to definitively attribute any positive outcome to ILE alone.

However, while the level of evidence is very low, the risk/benefit ratio in cardiac arrest favors the use of ILE with bupivacaine and the voting panel had strong agreement for this indication. There are no data to allow an informed decision on which resuscitative medication to use first among sodium

Table 2. Strength of recommendation and level of evidence.**Strength of recommendation (consensus-based)**

Level 1: Strong recommendation (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)

Level 2: Weak/conditional recommendation (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)

Neutral position: The course of action is neither preferred nor rejected by the majority of experts; either due to a balance in the desirable and undesirable effects of adherence to the recommendation or due to major uncertainties to its evaluation.

No recommendation: The group of experts reached no agreement

Level of evidence (GRADE system)

Grade A: High level of evidence (The true effect lies close to our estimate of the effect.)

Grade B: Moderate level of evidence (The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.)

Grade C: Low level of evidence (The true effect may be substantially different from our estimate of the effect.)

Grade D: Very low level of evidence (Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.)

bicarbonate, epinephrine, or ILE. Some members pointed out that if the total dose administered is within the known therapeutic range and the route of exposure is clearly not intravascular, consideration of an allergic reaction to LA rather than LA systemic toxicity probably warrants the use of epinephrine first. Because of a lack of evidence for the use of ILE with other LAs, the voting panel was unable to provide a firm recommendation in the setting of cardiac arrest. However, several members noted that harm appears to be low and there was a strong agreement for a neutral vote. Concerns about reports of an unclear interaction with concurrent administration of epinephrine or other resuscitative medications with ILE reported mainly in the local anesthetics literature may explain the voting panel's reticence to advise on ILE administration during cardiac arrest associated with non-bupivacaine LA toxicity.[10–13] Data were insufficient to make an evidence-based recommendation for the use of ILE with other LAs. In comparison with bupivacaine, both the lipophilicity and toxicity profiles of the other LAs vary considerably, thereby invalidating recommendations made by analogy rather than data.

- In life-threatening toxicity due to bupivacaine, we suggest using ILE as part of treatment modalities (2D) and we recommend its use if other therapies fail/in last resort (1D).

Rationale: The voting panel had strong agreement in concluding that there are enough data to support the use of ILE as a part of treatment modalities for patients with life-threatening bupivacaine toxicity. Moreover, while the risk/benefit ratio of this therapy is warranted if all other treatment modalities fail, the lack of data to guide the sequence of administration of resuscitative therapies made it impossible to decide on whether ILE should be the first-line treatment. Some members of the voting panel were concerned that waiting for other therapies to fail may decrease the potential efficacy of ILE and thus it should be given relatively early,

while there was consensus to use ILE if a patient was already unresponsive to other treatments.

- In life-threatening toxicity due to other LAs, we suggest using ILE if other therapies fail/in last resort (2D).

Rationale: There is a lack of convincing data for efficacy of ILE with other LAs. Despite this, there is a relatively favorable risk/benefit ratio in cases of prolonged toxicity in patients with a pulse but unresponsive to other treatments. As a result, the voting panel agreed that ILE could be used if other therapies fail or as a last resort. However, it was noted that in only a minority of reported cases ILE was used as sole treatment.

- In non-life-threatening toxicity due to bupivacaine or other LAs, our recommendation is neutral regarding the use of ILE.

Rationale: The voting panel agreed that, in this situation, there is equipoise between risk and benefits. There are not enough data reported to make an evidence-based decision.

Lipid regimen**1. ILE formulation:**

- When ILE is indicated for bupivacaine and other LAs toxicity, we suggest using the brand Intralipid® 20% (2D).

Rationale: Most of the data reported used this specific ILE formulation. The voting panel agreed that there were insufficient data to discuss other formulations in human poisonings until such time as comparative studies are reported.

2. ILE dosing:

- When ILE is indicated for bupivacaine and other LAs toxicity, our recommendation is neutral regarding the choice of ILE dosing.

Rationale: Although the voting panel agreement was for a neutral position, there was a slight preference for the most commonly reported dosing regimen: a bolus of 1.5 mL/kg and an infusion of 0.25 mL/kg/min of 20% ILE. Data are lacking with regards to ILE dose–response relationships for treating any human toxicity. No studies evaluated the benefit of an infusion after bolus vs. a bolus alone for toxins with a rapid endogenous clearance compared with most other toxins. The literature reports a varied range of bolus doses, infusion rates, and durations that make analysis of the optimal dosing regimen impossible.

3. ILE cessation:

- When ILE is indicated for bupivacaine and other LAs toxicity, our recommendation is neutral regarding which endpoints to use to stop ILE administration (maximum dose or maximum duration).

Table 3. Executive summary of indications regarding the use of ILE in poisoning.

Toxins	Clinical situations (strength of recommendation & level of evidence) ^a
<i>Local anesthetics</i>	
Bupivacaine	In cardiac arrest: we recommend using ILE (1D) In life-threatening toxicity: we suggest using ILE as part of treatment modalities (2D) and we recommend using ILE if other therapies fail/in last resort (1D) In non-life-threatening toxicity: neutral recommendation
All other local anesthetics	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D) In non-life-threatening toxicity: neutral recommendation
<i>Non-local anesthetics</i>	
Antidysrhythmics Class 1	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Amitriptyline	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE as part of treatment modalities (2D)
Other tricyclic antidepressants	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D)
Baclofen	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Beta receptor antagonists (Lipid-soluble)	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Beta receptor antagonists (Non lipid-soluble)	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Bupropion	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Calcium channel blockers: Diltiazem and verapamil	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Calcium channel blockers: Dihydropyridines	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D)
Cocaine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Diphenhydramine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE otherwise (2D)
Other antihistamines	Insufficient data
Ivermectin	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other insecticides	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Lamotrigine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Malathion	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other pesticides	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Olanzapine	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other antipsychotics	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Selective serotonin reuptake inhibitors	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)

^aNeutral position if not otherwise specified.

Rationale: The voting panel attempted to define endpoints for ILE treatment either with a maximum dose administered, a maximum duration of administration, or with resolution of toxicity. Members expressed opinions that a maximum dose should not be exceeded due to concerns about adverse effects from lipid overload. There were no strong data to inform the threshold amount of ILE that results in lipid toxicity. To avoid lipid overload, it was suggested from the voting panel that ILE doses should be limited to a maximum of 10% of total blood volume to limit possible complications arising from increased triglyceride concentrations in excess of 15 mmol/L (glycerol-blanked method) reported when ILE represented more than 10% of test tube volumes.[14] This is also to avoid fluid overload, which is an increasing concern in resuscitation as patients receiving ILE will likely have received other fluid solutions.[15] This is particularly of concern when administering ILE to obese patients, neonates, or young children. Assuming ILE remains mostly in the intravascular compartment, this rationale would indicate a total ILE dose of 560 mL for a 70 kg adult patient with an estimated blood volume of 5.6 L.

Also, given the pharmacokinetics of LAs and the lack of historical data to indicate a recurrence of toxicity once clinical improvement occurs, resolution of toxicity may be considered as an appropriate endpoint. The risk of prolonged ILE therapy on immune function or other organ function is as yet undefined for infusions administered for less than 24 h. However, some members were of the opinion that waiting to see a sustained improvement in the clinical status would be inadvisable, until such a time that studies report a benefit for continuation of therapy beyond the point of clinical resolution.

There is no strong evidence guiding the maximum duration of ILE therapy that could be safely administered if clinical improvement does not occur. However, the voting panel commented that clinical protocols for the use of ILE should recommend a specific duration and maximal volume of therapy to avoid administration of high doses of ILE over indefinite periods. This should take into consideration the adverse effect profile and the maximum duration of ILE recommended during parenteral nutrition.[16] As most articles reported use of ILE for 20–30 min, it seems reasonable to limit the duration of infusion to this time period until controlled experiments are published assessing specific treatment durations. Thus, the voting panel concluded that not enough evidence exists to inform on when to stop ILE.

Recommendations for non-local anesthetics

Amitriptyline and other tricyclic antidepressants

Indications:

- In cardiac arrest due to either amitriptyline or any other tricyclic antidepressants toxicity, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to amitriptyline, we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D).

- In life-threatening toxicity due to other tricyclic antidepressants, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to amitriptyline, we recommend not using ILE as first-line therapy (1D) and furthermore we suggest not using ILE as part of treatment modalities (2D).
- In non-life-threatening toxicity due to other tricyclic antidepressants, we suggest not using ILE in any circumstances (2D).

Rationale: One human RCT (published only in abstract and not specifying which TCAs were involved) failed to show a benefit of ILE on the duration of cardiotoxicity when patients were randomized to standard treatment with bicarbonate or ILE.[17] This explains why ILE therapy is discouraged either as first-line therapy either in life-threatening toxicity or with non-life-threatening toxicity. However, the situation of whether ILE might be beneficial in cases refractory to standard therapy, including epinephrine and bicarbonate therapy, was not explored. Many human case reports exist with inherent publication bias. However, the voting panel noted that some animal experiments, including one with an orogastric-poisoning model most similar to the clinical poisoning reported no benefit and possibly even harm.[18] Decades of published evidence for the efficacy of bicarbonate therapy exist. Thus, the panel voted for the use of ILE only in life-threatening toxicity from amitriptyline after failure of standard therapies, with moderate agreement.

Beta-receptor antagonists

Indications:

- In cardiac arrest due to toxicity of both lipid soluble and non-lipid soluble beta-receptor antagonists, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to lipid soluble beta-receptor antagonists, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to non-lipid soluble beta-receptor antagonists, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to lipid soluble beta-receptor antagonists, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to non-lipid soluble beta-receptor antagonists, we suggest not using ILE as first-line therapy nor as part of treatment modalities (2D).

Rationale: The voting panel had consistent agreement in their votes. Reasons cited for the results are the balance existing between risks and expected benefit of using ILE, the evidence for the safety and efficacy of high dose insulin euglycemia therapy and the possible use of extracorporeal assist devices reporting problems with concurrent ILE use. Moreover, the distinction between lipid-soluble and non-lipid soluble drugs, which were initially divided into two distinct categories to account for differences in log *D* did not

influence the voting panel's evaluation, except in cases of life-threatening toxicity where benefits were not considered to outweigh risk for non-lipid soluble beta receptor antagonist toxicity as a first-line therapy or in non-life-threatening toxicity as part of treatment modalities.

Bupropion

Indications:

- In cardiac arrest due to bupropion toxicity, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to bupropion, we suggest using ILE if other therapies fail/in last resort (2D), but we suggested not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to bupropion, we suggest not using ILE as first-line therapy (2D).

Rationale: Few case reports exist with survival outcome and it is unclear if the patients would have survived without ILE. However, the voting panel mentioned the likelihood of publication bias. Also, most cases of bupropion toxicity do well with non-specific therapies aimed at maintaining vital functions. Several case reports demonstrate improvement with bicarbonate therapy. It is unclear whether higher doses of bicarbonate, a medication with an established safety profile, would yield similar outcomes to ILE. More controlled data are needed to inform on whether or not ILE interferes with the efficacy of standard therapies such as benzodiazepines or barbiturates for seizures. The concurrent use of ILE and other therapies has not been studied in any detail. However, in the situation of prolonged and refractory status epilepticus, a trial of ILE seems reasonable. Hence, a 2D recommendation was made for cases with life-threatening toxicity if other therapies fail. However, in pulseless cardiac arrest, the voting panel felt ILE was not indicated given the reported interference it has on the effect of epinephrine or extracorporeal treatments. Hence, there was not a favorable enough risk/benefit ratio. Once ROSC (return of spontaneous circulation) is achieved, then ILE is suggested if life-threatening toxicity persists.

Calcium channel blockers

Indications:

- In cardiac arrest due to toxicity from calcium channel blockers (including diltiazem, verapamil and dihydropyridines), our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to diltiazem, verapamil, or dihydropyridine calcium channel blockers, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to diltiazem verapamil, or dihydropyridine calcium channel blockers, we suggest not using ILE as first-line therapy (2D).

Rationale: Due to the inconsistent outcomes reported, ranging from sudden death to immediate response, in both

animal experiments and human case reports, no clear recommendation can be made. Some members felt cardiac arrest presents a situation where little harm seems to exist for a "trial" of ILE. However, as noted above, other members expressed their concerns that ILE can enhance intestinal absorption of toxins as is demonstrated in oral drug poisoning models.[19] In addition, problems associated with the concurrent use of ILE with extracorporeal assist devices and the potential for interference with resuscitative medications with evidence of benefit, such as vasopressors and insulin-glucose, were also highlighted. A single study that mimicked an oral overdose of verapamil demonstrated worse outcomes when ILE was given. Animal studies showed no clinical benefit or benefit at dose requirements exceeding a dose of 12 mL/kg of 20% ILE.[19,20] No studies comparing the current standard of care with vasopressors or insulin-glucose therapy are available in a model consistent with human clinical poisoning. Considering the lack of information on dose, potential adverse effects and especially interference with extracorporeal assist devices or interference with medications known to be effective, the voting panel determined that the benefits were probably equal to the risks and thus, a neutral position resulted in the presence of cardiac arrest.

Unless organ perfusion is compromised, the voting panel felt that there was not enough information to make a decision and at the very least a balance exists between risks and potential benefits of ILE. Thus, there is a question as to whether ILE should be a part of the treatment modalities or used after standard therapy fails (last resort) in life-threatening toxicity for all calcium channel blockers.

Furthermore, the reason for not suggesting lipid emulsion if other therapies fail, in cases of non-life-threatening toxicity due to diltiazem and verapamil, and not suggesting ILE in all other circumstances of non-life-threatening toxicity due to dihydropyridines, is based on a risk/benefit analysis. Certain signs and symptoms of CCB toxicity, such as ileus or bradycardia and hypotension, may not respond or entirely correct with various therapies but only resolve with time and metabolism of the toxicant.

Cocaine

Indications:

- In cardiac arrest due to cocaine toxicity, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to cocaine, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to cocaine, we suggest not using ILE as first-line therapy (2D) or as part of treatment modalities (2D).

Rationale: Too few case reports exist, all with varied outcome to make a favorable recommendation. Several experimental studies with cocaine and ILE using pre-treatment animal models [21,22] were excluded a priori due to the lack of generalizability to the clinical setting of human cocaine poisoning. The voting panel was in agreement on a neutral

recommendation concerning the use of ILE in cardiac arrest and commented there was a paucity of data on the efficacy of ILE to reverse signs and symptoms of cocaine toxicity. The body of evidence and published experience with other treatments such as sodium bicarbonate, and benzodiazepines is much greater than that for ILE therapy. More controlled data are needed to assess whether or not ILE interferes with the efficacy of the standard therapies.

Diphenhydramine

Indications:

- In cardiac arrest due to diphenhydramine toxicity, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to diphenhydramine, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to diphenhydramine, we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE otherwise (2D).

Rationale: Due to the efficacy of bicarbonate therapy and the lack of superiority of ILE over bicarbonate reported in one animal experiment, the voting panel concluded there was no scenario where ILE would be clearly indicated at this time. There are no data to inform on the best timing of ILE administration. Diphenhydramine possesses sodium channel blocking properties and a trial of ILE has clinical equipoise when considering the possible risks of an acute administration of ILE in cases otherwise unresponsive to repeated administration of sodium bicarbonate (e.g. more than 200 mEq [23]). However, the role of ILE in non-life-threatening toxicity, such as anticholinergic delirium, was not reported in the literature at all.

A comment was made regarding the use of ILE with “other antihistamines”. It was noted that if the lipid sink or conduit theories proves to be valid, there might be a theoretical benefit for ILE in severe toxicity from sedating antihistamines. In particular, those agents with a log *D* value of 2 or 3 when other therapies have failed. However, more than 70% of the panel voted that there were insufficient data to consider recommendations in the category “other antihistamines”. This made it impossible to make a statement about any particular antihistamine, as described in the methodology.

Lamotrigine

Indications:

- In cardiac arrest due to lamotrigine toxicity, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to lamotrigine, we suggest not using ILE as first-line therapy (2D).
- In non-life-threatening toxicity due to lamotrigine, we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D).

Rationale: The voting panel determined that too few case reports exist with survival outcome reported. It is also unclear

if these patients would have survived without ILE. Additionally, the voting panel mentioned publication bias and the fact that most cases of lamotrigine toxicity do well with supportive care. More controlled data are needed to inform clinicians on whether or not ILE interferes with the efficacy of the standard therapies such as benzodiazepines and sodium bicarbonate to reverse the proconvulsant and sodium channel blocking properties of lamotrigine. Severe lamotrigine poisoning can also result in metabolic acidosis and acute kidney injury, which may require dialysis. The concurrent use of ILE and other therapies has not been studied in enough detail to provide comment. Of note, as described in our adverse effect review article,[5] the use of ILE with any extracorporeal circuit such as occlusion of the circulation.

Other toxins

This section includes the other toxins and categories of toxins for which the voting results were similar. Therefore, rather than lengthy individual statements, the results are discussed in aggregate. Once again the readers are referred to the [Appendices](#) and tables for a complete record of the voting.

- In cardiac arrest due to toxicity of Class 1 Vaughan–Williams antidysrhythmics, baclofen, ivermectin and other insecticides, malathion and other pesticides, olanzapine and other antipsychotics, and selective serotonin reuptake inhibitors, our recommendation is neutral regarding the use of ILE.
- In life-threatening toxicity due to other insecticides, malathion and other pesticides, olanzapine, and other antipsychotics, we suggest not using ILE as first-line therapy (2D).
- In life-threatening toxicity due to Class 1 Vaughan–Williams antidysrhythmics, baclofen, ivermectin, and selective serotonin reuptake inhibitors, our recommendation is neutral regarding the use of ILE.
- In non-life-threatening toxicity due to Class 1 Vaughan–Williams antidysrhythmics, baclofen, ivermectin, and other insecticides, malathion and other pesticides, olanzapine and other antipsychotics, and selective serotonin reuptake inhibitors, we suggest not using ILE as first-line therapy (2D).

Rationale: Even though some of these toxins are lipid-soluble (defined by their log *D*) due to the paucity of data, the panel primarily considered possible benefit, possible risks, and the availability of other alternative treatments in their votes.

Animal data provide conflicting results for the pesticide and insecticide groups. Thus, adverse effects and potential interferences were a major consideration influencing the voting. Moreover, these toxins represent a heterogeneous group of chemicals that are not amenable to a common statement on treatment with ILE. Antipsychotics rarely cause significant cardiovascular mortality and status epilepticus is uncommon. Class 1 antidysrhythmics produce their toxic effect by blocking sodium channels and no studies have compared bicarbonate to ILE for these drugs. The controversy surrounding

efficacy, the adverse effect profile, and the potential interferences with essential laboratory testing question the inclusion of ILE in the care of these poisonings. Clinically relevant studies with clear meaningful endpoints and drug concentration measurements to assess the toxic burden are required before stronger recommendations can be made for these toxins. Thus, the panel vote resulted in a neutral recommendation, leaving the decision to the clinician to weigh the pros and cons of ILE in these situations.

Lipid regimen

The panel chose to vote on a preferred lipid regimen for each category of toxins. However, the results were not significantly different from one toxin to another. In all cases, the vote was neutral with the median ranging from 4 to 6 and the disagreement index always below 1, reflecting the consensus among panel members.

1. ILE formulation:

- When ILE is indicated in non-LAs toxicity, our recommendation is neutral regarding the formulation of ILE.

Rationale: Not enough data exist comparing various formulations of ILE. Most articles do not report the brand of ILE used and simply list a concentration of 20%. There is no evidence to support a recommendation for the best formulation of ILE for non-LAs, even though the most common formulation used was Intralipid® 20%. While there is experimental evidence suggesting that one lipid formulation might be preferable to another, it is unclear if the relationship is true for all toxins or is applicable to human poisonings.[24]

2. ILE dosing:

- When ILE is indicated in non-LAs toxicity, our recommendation is neutral regarding the dosing of ILE.

Rationale: In the only ILE dose-finding study, the greatest benefit to survival in a rodent model of IV verapamil toxicity occurred with an ILE dose of 18.6 mL/kg.[20] However, the greatest benefit to HR, MAP occurred at 24.8 mL/kg ILE. It is unknown how these doses would translate to human poisonings. Additional concern was expressed over the IV model of poisoning and the risk for lipid-induced increase in gastrointestinal absorption, as noted above. Nevertheless, the finding that increased survival occurred in the group treated with a lower dose of ILE suggests that a higher dose, although associated with greater hemodynamic improvement, may not be necessary in all cases.

Members expressed opinions that until the adverse effect profile for acute ILE administration is properly defined, the lowest possible dose should be used. ILE dosing should be guided by clinically significant physiological endpoints, rather than arbitrary hemodynamic parameters. Importantly, analytical interferences are likely to be shorter in duration or less significant if a lower blood concentration of ILE is

achieved.[1] The maximum safe dose of ILE is unknown. Moreover, the reported ILE regimens may vary significantly from the commonly recommended regimen of 1.5 mL/kg bolus of ILE 20% followed by 0.25–0.5 mL/kg/min.[25,26] For a 70 kg person, this dose translates to more than 1 L of lipid emulsion in the first hour at the lowest rate and more than 2 L if the highest infusion rate (0.5 mL/kg/min) is administered. Parenteral nutrition guidelines limit the daily amount of ILE to between 500 and 1200 mL per 24-h period or 10 mL per kg of a 20% formulation.[27] Several reports cite a single rodent study assessing the apparent safety and LD₅₀ of ILE in nine rats.[28] The LD₅₀ is an imperfect measure of safety. Also, this study only included one ILE dose within the range currently used in the clinical setting. No studies have assessed varying doses and infusion rates or their combinations in humans.

The panel agreed that a maximum dose (per kg body weight) should be specified and the rate of infusion kept low. Termination of the infusion should be considered when there is sustained clinical improvement or the maximum dose has been reached. This is speculative and dose-finding studies are much needed. A recent publication called into question cases where exceedingly large volumes of ILE were used and created a pharmacokinetic–pharmacodynamic model to predict an infusion rate that would only produce “modestly lipemic plasma”. Although, based on their model, these authors recommend a regimen of 1.5 mL/kg followed by 0.25 mL/kg/min for 3 min and then an infusion of 0.025 mL/kg/min for up to 6.5 h,[29] this regimen should be validated for safety and efficacy before it can be routinely recommended.

3. ILE cessation:

- When ILE is indicated in non-LAs toxicity, our recommendation is neutral regarding which endpoints to use to stop ILE administration (maximum dose or maximum duration).

Rationale: The group reached consensus that there is insufficient information to determine when ILE should be stopped. The literature is heterogeneous in the endpoints to therapy from resolution of symptoms to an arbitrary decrease of serum TCA concentration resulting in duration of therapy of up to several days.[30] No clinical studies exploring different endpoints to therapy have been published to date. The workgroup suggests that clinical resolution is a desirable endpoint if toxicity is unlikely to recur, but if this endpoint takes time, consideration should be made not to exceed the rate of endogenous triglyceride metabolism as discussed above. The group noted that in many of the reports ILE was started along with other therapies and continued for hours or days even though the effect of ILE was unclear. The workgroup could not find evidence to suggest a specific endpoint. However, adverse effects seem to be associated with higher volume and faster infusion rates of ILE.[3] Analytical interferences and inability to measure several biochemical parameters and the unknown effect of ILE on other medications may justify lower doses and a shorter duration of infusion.[1]

Limitations

Despite the fact that our combined search strategies were exhaustive and not limited by language, it is possible that some publications were missed; especially abstracts not yet published as full articles. The literature infrequently reports the concentration of the toxin, precise timing of interventions with regards to clinical improvement or important information on the formulation, or total amount of ILE given. Also, in most case reports, multiple therapies were administered simultaneously, making the specific efficacy of lipid emulsion difficult to ascertain. Case reports are known to be subject to publication bias. We also noticed the majority of publications failed to mention the presence or absence of adverse effects and when events occurred there was a tendency to attribute them to the toxin rather than the therapy. Our clinical appraisal for the non-LA toxins was limited because most of the controlled studies occurred in animals and the majority were not performed with models bearing any resemblance to clinical poisonings, which usually involve ingestion of the toxin. The greatest limitation of these recommendations may be their reliance on published data which is often of poor quality, may have significant publication delay of up to several years, and cannot capture the vast numbers of positive and negative outcomes of ILE that remain unreported. Additionally, it should be noted that the Delphi method is itself imperfect, with the greatest criticism being its tendency to force "middle-of-the-road" consensus.[31] We feel we have addressed this concern in three ways: limiting the number of rounds of voting to two, in order not to artificially force consensus by repeated regression to the mean, using a disagreement index to demonstrate the true strength of the recommendations, and the inclusion of minority opinions in the comments and rationale when they were provided by the workgroup members. Also, patients' views and preferences were not directly sought in the development of the clinical recommendations due to the highly heterogeneous target population under study. Finally, as the study and clinical use of ILE continues to evolve, we recognize additional information may emerge to alter this analysis.

Discussion

Despite some early enthusiasm for the use of ILE in the treatment of acute poisoning, the voting panel found an absence of evidence to recommend its use in most poisonings and clinical scenarios where its use is previously reported. Thus the preponderance of neutral votes likely represents the workgroups' caution to make recommendations for or against a therapy where so little moderate- or high-quality human data exist. Furthermore, it is worth reiterating that the neutral recommendations result from a balance between pro and con assessments (rather than a lack of data which would result in no recommendation at all) but rather; based on disagreement index, represent a strong consensus around neutrality.

Moreover, many specific aspects of ILE therapy have not been validated in the clinical setting. These include the

optimal dose of ILE for clinical efficacy, the threshold dose for adverse effects, and the minimum or maximum duration of therapy. It is acknowledged that clinicians may have personal preferences for indication, dose, and duration of ILE treatment. Given that there is a lack of evidence to support any particular approach, the workgroup felt that it reasonable to comment that the most common formulation reported was Intralipid® 20%, and that the most common regimen was a bolus of 1.5 mL/kg of ILE 20% followed by an infusion of 0.25 mL/kg/min, in order to provide some guidance in situations where favorable recommendations or suggestions were made. Additionally, the workgroup recognized the lack of data on which to guide the duration of therapy, and, therefore, some members proposed a maximum dose of 10% of blood volume based on safety concerns but this position was not officially voted upon. This is somewhat in keeping with parenteral nutrition recommendations to limit the maximum dosage of ILE between 10 and 12.5 mL/kg/d of 20% ILE [32] as well reported increased triglyceride concentrations in excess of 15 mmol/L (glycerol-blanked method) when ILE represented more than 10% of test tubes volumes,[14] which for a 70 kg individual with a blood volume of 80 mL/kg would yield 8.0 mL/kg. Indications in which it is easier to measure the risk and benefit of ILE therapy, such as cardiac arrest or systemic toxicity with no other treatment alternatives, may warrant a "trial" of ILE therapy. Conversely, ILE should not be considered in clinical scenarios where the risk of death or organ damage is small, or when there are other accepted treatments, which have not been used first. Concern was expressed as to the lack of data regarding the impact of ILE on the effectiveness of other resuscitative medications or antidotes, or the ability of ILE to interfere with the biochemical and drug assay testing. In addition, outcome data from animal models may not be directly translatable to clinical practice. Notably, the majority of animal studies of ILE efficacy administered toxins intravenously, whereas the majority of clinical poisonings (except for local anesthetics) are the result of oral exposure.

Future research questions

The voting panel is hopeful that randomized controlled trials will be undertaken to enable a more informed evaluation of the role of ILE in select poisonings. Efforts in animals should be directed at designing controlled studies evaluating the timing of administration, using orogastric administration of the toxin. In particular, studying the dose-response relationship for the loading-dose and the infusion is important, while clearly reporting on the presence or absence of adverse effects. Ideally, these studies would also focus on determining the optimal endpoint for ILE therapy. *In vitro* studies may be sufficient to evaluate the potential interferences of ILE on assays of common co-ingestants or binding affinity with other medications. Moreover, the efficacy of commercially available lipid emulsions should be compared in order to determine

the relative effectiveness of the commercially available products.

Conclusion

ILE is a recent therapy for which there is an incomplete understanding of its efficacy, mechanisms of action, safety, and associated analytical interferences. Clinical recommendations regarding the use of ILE in poisoning were only possible in a small number of scenarios based on a very low quality of evidence, balance of risks and benefits, and resource use. The workgroup emphasizes that human dose-finding and randomized controlled studies are required to advance knowledge of limitations, indications, adverse effects, effectiveness, and best regimen for ILE treatment.

External review

The American Academy of Clinical Toxicology, the American College of Medical Toxicology, the American Association of Poison Control Centers, the Asia Pacific Association of Medical Toxicology, the European Association of Poison Centres and Clinical Toxicologists, and the Canadian Association of Poison Control Centers endorsed these recommendations prior to publication.

Applicability

The recommendations will be circulated to the membership of each association, published in a participating association's sponsored-journal and presented at international conferences.

Planned update

These recommendations are to be updated in 5 years unless new data warrants an earlier review.

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Appendix 1: Voting statements

General statement

Lipid emulsion is indicated in the treatment of XYZ toxicity.

Specific indications

Lipid emulsion is indicated in the treatment of XYZ toxicity:

- In the presence of cardiac arrest, after Standard ACLS (CPR, airways) has been started
- In the presence of LIFE-THREATENING toxicity
 - Lipid emulsion should be administered as first line therapy
 - Lipid emulsion be administered as part of treatment modalities
 - Lipid emulsion should be administered if other therapies fail (last resort)
- In the presence of NON LIFE-THREATENING toxicity
 - Lipid emulsion should be administered as first line therapy
 - Lipid emulsion be administered as part of treatment modalities
 - Lipid emulsion should be administered if other therapies fail (last resort)

Types of ILE

The type of ILE to be used is ...

- Intralipid[®] 10%
- Intralipid[®] 20%
- Intralipid[®] 30%
- ClinOleic[®] 20%
- Lipofundin[®] 20%
- Other

If using a bolus of ILE the dose of the bolus indicated is ...

- 0.25 mL/kg
- 0.50 mL/kg
- 0.75 mL/kg
- 1.0 mL/kg
- 1.25 mL/kg
- 1.5 mL/kg
- 1.75 mL/kg
- 2.0 mL/kg
- Other

If using an infusion of ILE the dose of the infusion indicated is ...

- 0.25 mL/kg/min
- 0.5 mL/kg/min
- 0.75 mL/kg/min
- 1.0 mL/kg/min
- Other

Cessation of ILE

The decision to terminate the ILE treatment is indicated based on:

- Total (maximum) duration of the infusion regardless of dose or clinical improvement status
- Total (maximum) dose administered regardless of duration of infusion or clinical improvement status
- Clinical improvement regardless of dose or duration administered
- Other

In considering the total duration of the infusion as a criterion, lipid emulsion cessation is indicated, regardless of other factors such as clinical improvement or dose after ...

- 10–20 min
- 21–30 min
- 31–40 min
- 41–50 min
- 51–60 min
- Other

In considering the maximum dose of lipid emulsion administered as a criterion, lipid emulsion cessation is indicated, regardless of clinical improvement or duration after ...

- 8 mL/kg or less
- 8.1–10.0 mL/kg
- 10.1–12.0 mL/kg
- 12.1–14.0 mL/kg
- 14.1–16.0 mL/kg
- 16.1–18.0 mL/kg
- 18.1–20.0 mL/kg
- Other

In considering the clinical improvement as a criterion, lipid emulsion cessation is indicated, regardless of dose or duration after ...

- As soon as symptoms resolution occurred
- After resolution of symptoms for 15–30 min
- After resolution of symptoms for 31–45 min
- After resolution of symptoms for 46–60 min
- Other

Appendix 2

Literature update

Search results for the year 2015 update: 1026 citations were reviewed to identify studies reporting the use of ILE in poisoning (Figure 2). Of those, 942 were excluded after reviewing abstracts since the ILE administration was not related to poisoning. Of the 84 remaining articles, 28 were further excluded after reviewing complete manuscripts: one was excluded because ILE was not used for the treatment of poisoning, two were pre-treatment studies, one was an animal experiment that was not generalizable to humans, 18 were review articles without original data, two only reported survey information, and four did not present sufficient data for evaluation. A total of 56 studies were included in the update, from

which eleven were animal reports, two regarding LA and nine non-LA poisonings.[33–43]. Forty-five human reports, eight regarding LA and 37 non-LA were included.[44–88] A summary of the new included articles is presented in [Appendices 3 and 4](#).

Local anaesthetics

No new clinical trials were found in humans. Seven case reports and one case series reported a total of twelve cases.[44–51] The LAs reported were lidocaine ($n=2$), levobupivacaine ($n=1$), bupivacaine ($n=3$), ropivacaine ($n=3$), combination of bupivacaine and ropivacaine ($n=1$), and ropivacaine and lidocaine ($n=2$). Patients experienced LA toxicity from different routes of exposure: nerve block ($n=7$), intravenous ($n=4$), epidural ($n=1$), subcutaneous ($n=1$), and intrathecal ($n=1$) use. Two reports included two routes of LA exposure, intravenous plus epidural and intravenous plus subcutaneous. The toxic effects from LAs included a variety of cardiovascular and central nervous system symptoms including hypotension, cardiac arrest, agitation and coma. The concentration of ILE used was reported as 20% ($n=5$) or not reported ($n=7$). Dosing regimens and other treatments received were often not reported. In eight cases, authors noted that the symptoms resolved following ILE dosing. Details are provided in [Appendix 3](#).

Two controlled animal experiments in swine assessed the response of bupivacaine toxicity to ILE. In one trial, 12 swine were administered 4–6 mg/kg of bupivacaine until the QRS complex duration was 150% of baseline value. Six swine were then given ILE 1.5 mL/kg followed by 0.25 mL/kg/min and six were given the same volume of 0.9% saline as controls. All animals survived. QRS duration decreased from $184 \pm 62\%$ ms to $132 \pm 65\%$ ms in the ILE-treated group, while there was no change in QRS duration ($230 \pm 56\%$ ms) in the control animals ($p=0.03$).[34] The other trial included 30 swine, 10 serving as control, 10 receiving ILE as long-chain triglycerides (LCT) and 10 receiving ILE as 50% LCT and 50% medium-chain triglycerides (MCT). All animals were administered 5 mg/kg of bupivacaine followed by the study drug while monitoring hemodynamic parameters. A dose of 4 mL/kg of either ILE preparation or saline was administered to each group one minute after bupivacaine dosing. Both ILE groups had a similar improvement in the majority of the hemodynamic parameters compared to control.[33] Details are reported in [Appendix 4](#).

There were no new LA case reports described in animals.

Non-local anesthetics

No new clinical trials in humans were identified. Thirty-seven case reports or case series with miscellaneous toxins were found.[52–88] The summary of human case reports is presented in [Appendix 3](#).

Three animal experiments studied ILE for non-LA toxicity.[35,39,42] In one trial, 20 cats with 14 additional controls were exposed dermally to permethrin. ILE was administered to the treatment group at 15 mL/kg as a continuous intravenous infusion over 60 minutes. A grading system for neurologic effects detected a decrease in the duration and severity of poisoning in the treatment group reported as a decrease in the duration and severity of poisoning in the treatment group.[39] Another randomized experiment in swine sought to determine a difference in mean arterial blood pressure (MAP), QRS duration and survival after diphenhydramine poisoning. Twenty-four animals were equally divided into two groups. One group received ILE (7 mL/kg) and the other sodium bicarbonate. Diphenhydramine was administered intravenously until MAP fell by 50%. No differences were found between groups in the measured parameters.[42] In the third study, rats received intravenous propofol 10 mg/kg to achieve a $55\% \pm 2\%$ drop in MAP. The rats were not randomized but the study included a control group receiving saline. The authors reported that propofol-mediated hypotension was completely reversed by ILE, and the effects on the anaesthetic potency of the drug were minimal.[35] Of note, propofol was not chosen as a toxin to be evaluated for clinical recommendations by the workgroup because of the lack of human data. A summary of the animal case reports is available in [Appendix 4](#).

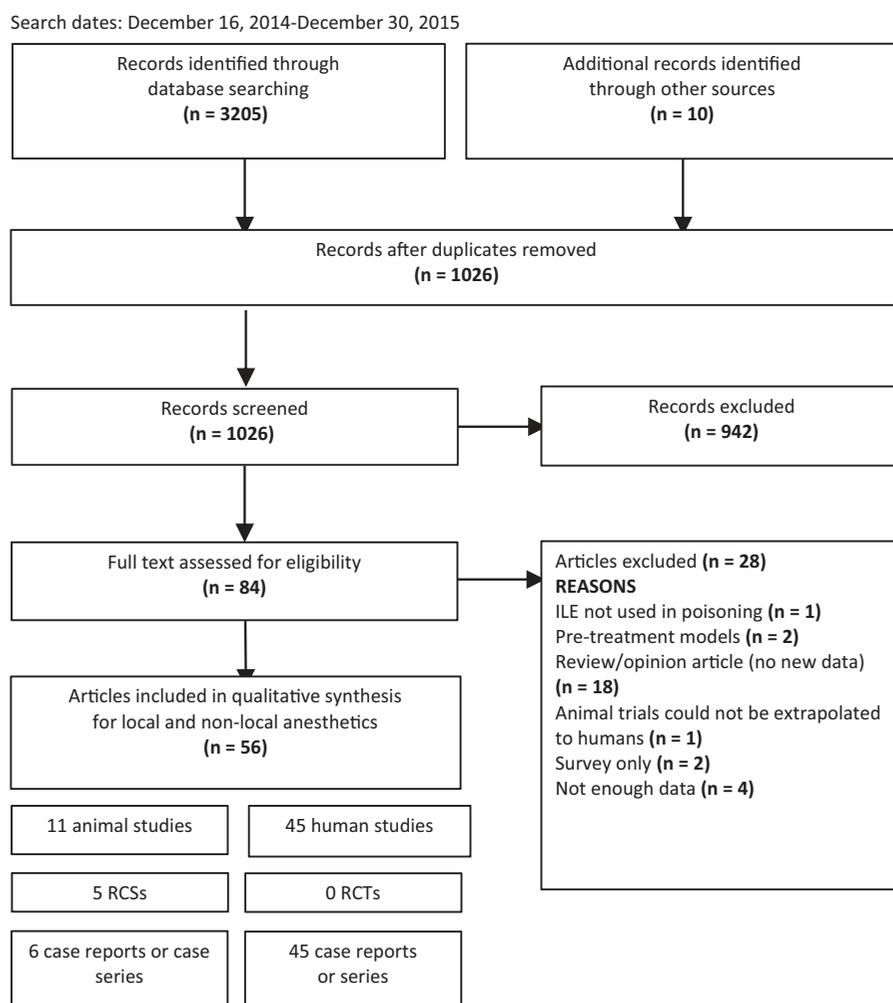


Figure 2. Selection of articles flow diagram for 2015 update. RCS: randomized controlled studies; RCT: randomized controlled trials; ILE: intravenous lipid emulsion.

Appendix 3. Summary of the 72 patients included in the 2015 update on the efficacy of ILE in poisoning.

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug concentration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^a	Other treatments received	ILE effect	Outcome
<i>Local anaesthetics</i> Glavas et al. [44]	Case report	64 y/F	Levobupivacaine 10 mg Epidural/Intravenous (amoxicillin)	2.68	Hypotension Coma	20%	200 mL	NR (total: 200 mL)	IV fluids, Pressors, Anesthetics, Atropine Epinephrine	Yes	Survival
Goucher & Asher ^b [45]	Case report	60 y/F	Lidocaine 18 mL 2% Intravenous	1.26	PVC Coma	NR	150 mL	NR (total: 150 mL)	Epinephrine Anesthetics	Yes; No hemodynamic compromise throughout Unclear if drug effect had just worn off; Neurologic symptoms improved after administration Unclear	Survival
Kamel et al. [46]	Case report	51 y/F	Bupivacaine 80 mL 5% Nerve block	2.68	Dizziness Agitation Posturing Loss of left lower extremity sensation Hypotension Bradycardia, asystole Cardiac arrest Apnea Coma	20%	100 mL	400 mL in 20 min (total: 500 mL)	Epinephrine, Anesthetics	Improved 30 min after ILE	Survival
Musiak & McCall [47]	Case report	6 y/M	Bupivacaine 3 mg/kg Subcutaneous/Intravenous	2.68	Hypotension Bradycardia, asystole Cardiac arrest Apnea Coma	NR	1.5 mg/kg ^f	0.25 mg/kg/min for 6 h (total: 91.5 mg/kg) ^f	Epinephrine, Pressors, (norepinephrine, epinephrine, vasopressin, phenylephrine)	Unclear	Survival
Procopio et al. [48]	Case report	43 y/M	Bupivacaine 10 mL Ropivacaine 30 mL Intrathecal	2.68 4.21	Hypotension Bradycardia Apnea Coma	20%	1.5 mL/kg	125 mL in 2 h (total: NR)	Pressors	Improved 30 min after ILE	Survival
Riff et al. ^d [49]	Case series, No 1	Age NR/sex NR	Ropivacaine 220 mg Nerve block [4.20 mcg/mL]	4.21	Coma Seizures Coma	NR	NR	NR	NR	Authors state "quick symptoms resolving"	NR
	Case series, No 3	Age NR/F, pregnant	Ropivacaine 150 mg Nerve block [4.80 mcg/mL]	4.21	Obrundation	NR	NR	NR	NR	Authors state "quick symptoms resolving"	NR
	Case series, No 4	Age NR/F, pregnant	Ropivacaine 100 mg Nerve block [0.66 mcg/mL]	4.21	Obrundation	NR	NR	NR	NR	Authors state "quick symptoms resolving"	NR
	Case series, No 7	Age NR/F, pregnant	Ropivacaine 40 mg [0.51 mcg/mL]	4.21	Seizure Mydriasis	NR	NR	NR	NR	Authors state "quick symptoms resolving"	NR
	Case series, No 8	Age NR/sex NR	Lidocaine 200 mg [1.01 mcg/mL] Nerve block Ropivacaine 40 mg [0.29 mcg/mL] Lidocaine 200 mg [0.58 mcg/mL]	1.26 4.21	Hypotension Bradycardia Metallic taste	NR	NR	NR	NR	Authors state "quick symptoms resolving"	NR
Shih & Calleb ^b [50]	Case report	56 y/F, weight NR	Lidocaine 30 mL 0.25% Nerve block	2.68	Hypotension Apnea Coma	20%	85 mL	NR (total: 85 mL)	IV fluids, Pressors, Anesthetics	Motor and sensory function improved over 4 h	Survival
Stella et al. ^b [51]	Case report	<1 week/NR	Lidocaine 6 mg/kg, then 6 mg/kg/h for 18 h, then 4 mg/kg/h for 12 h Intravenous	1.26	Lactate 4 mmol/L Bradycardia, wide QRS	20%	2 mL/kg	NR	NR	Wide QRS and bradycardia resolved	Survival
<i>Non-local anaesthetics</i> Agulnik [52]	Case report	15 y/F	Carbamazepine 56 g Oral ingestion [138 mcg/mL]	2.67	Status epilepticus Coma (induced with barbiturates, technically not from ingestion) Lactate reported as high	NR	NR	NR	Plasmapheresis, HDI, CWHD	Unclear	Survival

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug con- centration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^a	Other treatments received	ILE effect	Outcome
Aksel et al. [53]	Case series, No 1	35 y/M	Synthetic cannabinoid receptor agonists, dose and route NR (heroin)	NA	wide QRS 150 ms, left bundle branch block, sinus tachycardia 100 beats/min Coma pH 6.9	20%	1.5 mL/kg	0.25 mL/kg/h for 1 h (total: 1155 mL)	IV fluids	QRS narrowed within 5 min after ILE bolus improved in an unknown timeframe	Died
	Case series, No 2	19 y/M	Synthetic cannabinoid receptor agonists, dose NR Smoking	NA	Hypotension 70/30 mmHg Sinus bradycardia 42 beats/min	20%	1.5 mL/kg	0.25 mL/kg/h for 1 h (total: 990 mL)	IV fluids	Hemodynamics improved	Survived
	Case series, No 3	15 y/M	Synthetic cannabinoid receptor agonists, dose NR Smoking	NA	Hypotension 80/40 mmHg Sinus bradycardia 36 beats/min Coma	20%	1.25 mL/kg	0.50 mL/kg/h for 1 h (total: 2100 mL)	IV fluids	Hemodynamics and coma score improved	Survived
	Case series, No 4	17 y/M	Synthetic cannabinoid receptor agonists, dose and route NR	NA	Accelerated junctional rhythm, bigeminy	20%	1.5 mL/kg	0.25 mL/kg/h for 1 h (total: 990 mL)	IV fluids	Hemodynamics improved	Survived
Barton et al. [54]	Case report	59 y/M	Metoprolol 7.5 g Oral ingestion [120 ng/mL] (methamphetamine, ketamine, caffeine) Aluminum phosphide 3 g Oral ingestion	-0.34	Hypotension 74/43 mmHg Bradycardia 50 beats/min, atrial fibrillation Cardiac arrest Apnea Sinus tachycardia 100 beats/min Respiratory rate 30/min pH 7.33	20%	1.5 mL/kg (1st dose), 150 mL (2nd dose)	No (total: NR)	IV fluids, Pressors, H1ET, atropine, glucagon	ILE was given at the same time as ACLS and H1ET. ROSC and opened eyes	Survival
Banuah et al. [55]	Case series, No 1	40 y/F	Aluminum phosphide 3 g Oral ingestion	NA	Hypotension 80/60 mmHg Sinus tachycardia 100 beats/min Respiratory rate 34/min pH 7.081	20%	No	10 mL/h (total: NR)	Gastric lavage, Magnesium sulphate	Hemodynamics improved over time	Survival
	Case series, No 2	30 y/M	Aluminum phosphide 3 g Oral ingestion	NA	Hypotension 85/55 mmHg Sinus tachycardia 132 beats/min Respiratory rate 34/min pH 7.081	20%	No	10 mL/h (total: NR)	Gastric lavage, Magnesium sulphate	Hemodynamics improved over time	Survival
Bayram et al. [56]	Case report	21 y/F	Propafenone 1500 mg Oral ingestion (acetaminophen, acetyl salicylic acid)	2.39	Hypotension Bradycardia, wide QRS >200 ms Cardiac arrest Single seizure Metabolic acidosis (details NR)	20%	1.5 mL/kg	0.25 mL/kg/h for 30 min (total: NR)	Sodium bicarbonate, IV fluids, Pressors	After cardiac arrest ILE narrowed QRS widening and improved hemodynamics	Survival
Besserer et al. ^b [57]	Case report	36 y/M	Timicosin phosphate, dose NR Accidental self injection	1.52	Hypotension	20%	100 mL	500 mL in 30 min (total: 600 mL)	IV fluids, Pressors, HDI	Unclear	Survival
Brunfield et al. [58]	Case report	33 y/F	Flecainide, dose NR Oral ingestion	0.55	Cardiac arrest Altered mental status	20%	100 mL (1.5 mL/kg)	900 mL/h (12 mL/kg/h) (total: NR)	Sodium bicarbonate, IV fluids	ILE was given after ROSC and then the patient required another VT arrest and ECMO NSR with hypotension, asystole at 12 h post- ingestion, then ROSC with hypotension, then ultimate recovery.	Survival
Christianson et al. ^b [59]	Case report	64 y/M	Diltiazem 19.4 g sus- tained release Oral ingestion	2.64	Hypotension Dysrhythmias Cardiac arrest Apnea Single seizure Coma	NR	NR	NR	IV fluids, Pressors, Anesthetics, HDI, calcium, glucagon, ECMO	Survival shock liver and still intubated on day 11 Unknown ILE timing	Survival

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route (Quantitative drug concentration) (congestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^a	Other treatments received	ILE effect	Outcome
Czetwonka & Heim ^b [60]	Case report	33 y/F	Atenolol, dose NR Oral ingestion (zolpidem, acetaminophen, ethanol)	-2.03	Hypotension Coma	NR	NR	NR	IV fluids, Pressors, Anesthetics HDI, blood products, activated charcoal, acetylcysteine, calcium	Unclear	Survival
Doepker et al. ^e [61]	Case series, No 1	35 y/M	Metoprolol 1180 mg Amlodipine 150 mg Verapamil 10.26 g ER Oral ingestion (insulin)	-0.34 2.00 2.91	Non-measurable blood pressure Bradycardic arrest <20 beats/min Coma	20%	1.5 mL/kg (130 mL)	0.25 mL/kg/min for 1 h (total: NR)	IV fluids, Pressors, HDI, atropine, calcium, glucagon	Authors note a benefit of ILE therapy for the amlodipine overdose	Survival
	Case series, No 2	59 y/M	Metformin 30 g Amlodipine 300 mg Lisinopril 300 mg Simvastatin, dose NR Oral ingestion	-5.44 2.00 -1.80 4.60	Hypotension 78/36 mmHg Bradycardia 54 beats/min Lactate 6.6 mmol/L, anion gap 17	20%	1.5 mL/kg (105 mL)	0.25 mL/kg/min for 1 h (total: NR)	IV fluids, Activated charcoal, dextrose, calcium, glucagon, HDI	Authors note a benefit of ILE therapy for the amlodipine overdose	Survival
Gerard et al. [62]	Case report	58 y/F	Amlodipine 480 mg Valsartan 3680 mg Oral ingestion	2.00 -0.34	Hypotension 78/57 mmHg Tachycardia 103 beats/min, QT 555 ms Lactate 18 mmol/L pH 7.23	20%	No	8 mL/kg for 10 min (total: 80 mL/kg)	IV fluids, Pressors, Calcium, HIET, methylene blue, MARS	Improvement was not seen with ILE, responded to the use of MARS	Survival
Hatten [63]	Case report	32 y/F	Quetiapine, dose NR Oral ingestion [5929 ng/mL] (heroin; positive, unknown matrix for morphine, oxycodone)	1.82	Hypotension Tachycardia, wide QRS > 160 ms (previous 92 ms) Cardiac arrest Apnea Coma Lactate 25 mmol/L pH 7.27	NR	NR	NR	Sodium bicarbonate, IV fluids, Pressors, Anesthetics, Naloxone	Hemodynamics did not change in relation to ILE, No complications reported to ILE	Died;
Johnson-Arbor et al. ^e [64]	Case report	43 y/F	Propranolol 12 g [3.5 mg/L after 23 h] Tramadol 1.5 g Zolpidem 200 mg Alprazolam 15 mg Acetaminophen, dose NR Oral ingestions	0.99 0.40 2.35 2.50 0.40	Cardiogenic shock, ejection fraction 20% Apnea Coma	20%	1.5 mL/kg x3	0.25 mL/kg/min (total: NR)	IV fluids, Pressors, Anesthetics, Insulin, Glucagon	No	Died, Laboratory evaluation impossible due to lipemia
Jovic-Stosic et al. [65]	Case series, No 1	24 y/F	Amlodipine 150 mg [0.05 mg/L] Metformin 10 g [6.32 mg/L] Gliclazide 2.4 g [3.95 mg/L] Oral ingestion	2.00 -5.44 0.16	Hypotension Dysrhythmias Cardiac arrest Lactate 4.9 mmol/L, pH 7.27	20%	100 mL	900 mL (total: 1000 mL)	IV fluids, Pressors, Anesthetics, Glucagon	Transient blood pressure improvement then none further	Died
	Case series, No 2	41 y/M	Nifedipine, dose NR [0.62 mg/L] Metoprolol, dose NR [0.57 mg/L] Diazepam, dose NR [1.04 mg/L] Oral ingestion	3.45 -0.34 3.86	Hypotension Dysrhythmias, type 2, then type 3 AV block Cardiac arrest Apnea Coma	20%	500 mL	NR (total: 500 mL)	IV fluids, Pressors, Calcium, Glucagon	No improvement in hemodynamics	Died

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug concentration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^b	Other treatments received	ILE effect	Outcome
Khan et al. [66]	Case report	31 y/F	Amlodipine, dose NR Losartan, dose NR Oral ingestion	2.00 1.61	Hypotension Apnea Coma	NR	NR	NR	IV fluids, Pressors, ECMO	No improvement with pharmacologic therapy	Survival
Laes et al. ^c [67]	Case report	61 y/M	Atenolol 500 mg Amlodipine 200 mg Losartan 375 mg Oral ingestion	-2.03 2.00 1.61	Hypotension; MAP 55 mmHg, ejection frac- tion 60-65% Lactate 4.5 mmol/L	20%	1.5 mL/kg	NR	Pressors, HIVET/CVHD, methylene blue 2 mL/kg in 30 min Sodium bicarbonate, IV fluids, Pressors	Minimal change in blood pressure or heart rate	Survival
Li et al. [68]	Case report	25 y/F	Diphenhydramine oral mixture, dose NR Oral ingestion	1.92	Hypotension Wide QRS 120 ms Status epilepticus	20%	Yes, dose NR	NR	IV fluids, Pressors	ILE given after other treatments failed and better <1 h with improved hemodynamics and narrowed QRS	Survival
Lookabill et al. ^b [69]	Case report	17 mth/F	Flecainide 100 mg Route NR	0.55	Hypotension 64/41 mmHg Wide QRS 162 ms Coma	20%	11 mL (1 mL/kg)	165 mL/h 0.25 mL/kg/min (total: NR)	Sodium bicarbonate	Unclear; Symptoms improved after concur- rent bolus of bicarbonate	Survival
Markota et al. [70]	Case report	66 y/M	Bisoprolol 450 mg Amlodipine 300 mg Doxazosin 200 mg Nifedipine 600 mg Torsemide 150 mg Acetyl salicylic acid 4000 mg Ibuprofen 5000 mg Oral ingestion	0.11 2.00 0.54 3.45 1.44 -1.69	Hypotension Coma Lactate 8.5 mmol/L pH 7.12	20%	100 mL	150 mL in 60 min (total: 250 mL)	IV fluids, Pressors, Calcium, Glucagon, HDI	Unclear Possible improvement coinciding with ILE	Survival
Matsumoto et al. [71]	Case report	24 y/F	Chlorpromazine 3 g Mirtazapine 990 mg Oral ingestion	3.42 2.40	Hypotension 80/50 mmHg Asystole Cardiac arrest Apnea Coma Lactate 138 mg/dL pH 7.13	20%	100 mL x2	No (total: 200 mL)	Pressors, ECMO	No response to 1st dose. ECMO initiated after ROSC 2 min after 2nd dose ILE	Survival
McBeth et al. [72]	Case report	23 y/F	Hydroxychloroquine 40 g Oral ingestion [6425 nmol/L at 12 h]	1.96	Hypotension 92/60 mmHg and declining Ventricular fibrillation, PQWT, QRS 140 ms, QT 576 ms Apnea Coma pH 7.33	20%	1.5 mL/kg	Dose NR, duration 30 min (total: 500 mL)	Sodium bicarbonate, IV fluids, Pressors, HD, calcium channel blocker	Authors report "improvement after ILE and HD"	Survival
Montague [73]	Case report	7 mth/F	Propranolol 108 mg Oral ingestion	0.99	Hypotension Bradycardia Coma	20%	No	1.5 mL/kg in 2 h (total: 1.5 mL/kg)	IV fluids, HIVET	Hemodynamics did not improve with ILE	Survival
Mukhtar [74]	Case report	13 y/F	Flecainide 900 mg Oral ingestion (bisoprolol, acetyl sali- cyclic acid)	0.55	Hypotension 70/39 mmHg VT, ventricular fibrillation, TdP, Brugada pattern Cardiac arrest Venous pH 7.55	20%	70 mL	225 mL in 20 min (total: 295 mL)	Sodium bicarbonate, IV fluids, Pressors, Glucagon	ILE given after ROSC for cardiac arrest not before	Survival
Ovakim et al. ^b [75]	Case report	21 y/F	Yew 250 mL cut leaves Oral ingestion	NA	Wide QRS, irregular heart rhythm Coma	NR	NR	NR	Sodium bicarbonate, IV fluids	No description of any changes after ILE	Survival

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug concentration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^b	Other treatments received	ILE effect	Outcome
Ozete et al. [76]	Case report	35 y/F	Propafenone 150 mg Oral ingestion	2.39	Hypotension Dysrhythmias, QRS 160ms Cardiac arrest Single seizure Status epilepticus Coma	NR	100 mL	0.25 mL/kg/h for 1 h (total: NR)	Sodium bicarbonate, IV fluids, Pressors, Atropine	Unclear	Survival
Radley [77]	Case report	NR/NR	Amitriptyline 4.8 g Oral ingestion (ethanol, venlafaxine, zopiclone)	3.96	Hypotension QTc prolongation 3 isolated seizures x3 pH 7.45-7.6	NR	NR	NR (total: 500 mL)	Sodium bicarbonate, IV fluids, Pressors, Midazolam	Improvement in MAP and decreased use of Pressors required late, but no toxin confirmation	Survival; ARDS on day 3
Reynolds & Judge [78]	Case report	24 y/F	Flecainide, dose NR Oral ingestion [11,085 ng/mL at 4 h]	0.55	Hypotension Bradycardia, wide QRS Cardiac arrest (PEA) Apnea Single seizure Status epilepticus Coma Lactate 4 mmol/L	20%	200 mL	No (total: 200 mL)	Sodium bicarbonate, IV fluids, Pressors	No effect of ILE	Survival
Sampson ^e [79]	Case report	24 y/F	Verapamil 7.2 g ER and 80 mg immediate-release Oral ingestion	2.91	Arterial pH 7.08 Hypotension 65/30 mmHg Tachycardia 80 beats/min	20%	60 mL IO and then 60 mL IV	No (total: 120 mL)	IV fluids, Pressors, Glucagon, HIET	No effect of ILE	Died (The patient reported pain during IO bolus infusion) NR
Schult et al. [80]	Case report	12 y/F	Amlodipine 240 mg (87 mg/mL) Benzapril 480 mg Oral ingestion	2.00 -0.71	Hypotension Coma	20%	100 mL	NR	NR	NR	Survived
Sebe et al. [81]	Case series, No 1	27 y/F	Diltiazem 2400 mg (40 mg/kg) Oral ingestion	2.64	Hypotension 2nd degree heart block	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, HIET, Temporary pacemaker	Normotensive after ILE	Survived
	Case series, No 2	21 y/F	Amlodipine 140 mg (1.86 mg/kg) Oral ingestion	2.00	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, HIET	Normotensive after ILE	Survived
	Case series, No 3	51 y/M	Metoprolol 1800 mg (30 mg/kg) Oral ingestion	-0.34	Cardiac arrest	20%	1.5 mL/kg x3	No (total: 4.5 mL/kg)	IV fluids, Glucagon, Mechanical ventilation	No improvement in hemodynamics	Died (ARDS)
	Case series, No 4	44 y/F	Valsartan 1600 mg (17.7 mg/kg) Oral ingestion	-0.34	Hypotension	20%	1.5 mL/kg x3	No (total: 4.5 mL/kg)	IV fluids, Calcium, HIET	No improvement in hemodynamics	Survived
	Case series, No 5	22 y/F	Amlodipine 90 mg (1.63 mg/kg) Oral ingestion	2.00	Hypotension	20%	1.5 mL/kg x3	No (total: 4.5 mL/kg)	IV fluids, Calcium, HIET	No improvement in hemodynamics	Survived
	Case series, No 6	32 y/F	Amlodipine 150 mg (1.76 mg/kg) Oral ingestion Acetaminophen (paracetamol)	2.00	3rd degree heart block	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, Acetylcysteine, Temporary pacemaker	Normotensive after ILE	Survived
	Case series, No 7	31 y/F	Amlodipine 110 mg (1.46 mg/kg) Oral ingestion	2.00	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, HIET	Normotensive after ILE	Survived
	Case series, No 8	23 y/F	Carvedilol 750 mg (12.5 mg/kg) Oral ingestion	3.16	Hypotension Bradycardia	20%	1.5 mL/kg x2	No (total: 3.0 mL/kg)	IV fluids, Glucagon, Temporary pacemaker	Normotensive after ILE	Survived

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug concentration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^b	Other treatments received	ILE effect	Outcome
	Case series, No 9	18 y/F	Verapamil 2880 mg (41.1 mg/kg) Oral ingestion	2.91	Cardiac arrest	20%	1.5 mL/kg x2	No (total: 3.0 mL/kg)	IV fluids, Calcium, HIET Mechanical ventilation	Normotensive after ILE	Hypoxic, ischemic encephalopathy
	Case series, No 10	21 y/F	Propranolol 960 mg (11.3 mg/kg) Oral ingestion	0.99	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Glucagon	Normotensive after ILE	Survived
	Case series, No 11	31 y/M	Amlodipine 210 mg (2.33 mg/kg) Oral ingestion	2.00	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, HIET	Normotensive after ILE	Hypoxic ischemic encephalopathy
	Case series, No 12	26 y/F	Carvedilol 625 mg (9.6 mg/kg) Oral ingestion	3.16	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Glucagon	Normotensive after ILE	Survived
	Case series, No 13	44 y/F	Verapamil 1320 mg (16.5 mg/kg) Oral ingestion	2.91	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Calcium, HIET	Normotensive after ILE	Survived
	Case series, No 14	24 y/M	Propranolol, dose NR Oral ingestion	0.99	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Glucagon	Normotensive after ILE	Survived
	Case series, No 15	33 y/M	Propranolol 800 mg (0.94 mg/kg) Oral ingestion	0.99	Hypotension	20%	1.5 mL/kg	No (total: 1.5 mL/kg)	IV fluids, Glucagon	Normotensive after ILE	Survived
Su ^b [82]	Case report	17 y/M	Amlodipine 1.25 g Oral ingestion (many coingestants (unspecific))	2.00	Hypotension 50/30 mmHg Bradycardia 40 beats/min, 3rd degree block	NR	NR	NR	IV fluids, Pressors, Calcium, Insulin, Glucagon, ECMO	Improvement was not seen with ILE, patient improved with ECMO	Survival
Szadkowski et al. [83]	Case report	12 mth/M	Flecainide, dose NR Route NR (2.57 mcg/mL)	0.55	Hypotension Dysrhythmias Apnea Coma	20%	1.5 mL/kg	0.25 mL/kg/h for 2 h. Then stopped for 30 min and then restarted	IV fluids, Pressors	VT recurred 30 min after 1st infusion ended, resolved after restarting ILE infusion and sodium bicarbonate.	Survival
Tse et al. [84] Note: Poison center study of a variety of toxins, 2nd hand information	Case series, No 1	45 y/M	Propranolol, dose NR Doxiepin, dose NR Oral ingestion	0.99 2.92	Cardiac arrest	20%	100 mL	NR	Sodium bicarbonate	Positive effect of ILE on ROSC	Survival
	Case series, No 2	46 y/F	Amitriptyline, dose NR Oral ingestion	3.96	QRS changes (details NR) Cardiac arrest	20%	100 mL	0.25 mL/kg/min for 30 min (total: NR)	Sodium bicarbonate, Pressors	Authors report "Effect on hemodynamics"	Survival
	Case series, No 3	45 y/F	Amitriptyline, dose NR Oral ingestion	3.96	Wide QRS	NR	No	0.25 mL/kg/min for 2 h	Sodium bicarbonate	NR	Survival
Tse et al. [85]	Case report	55 y/M	Methamphetamine "egg size" dose Oral ingestion	-0.57	Tachycardia Adrenergic symptoms	20%	1.5 mL/kg	NR (total: 1.5 mL/kg)	NR	Resolution of hyperadrenergic excess in 20 min	Survival
Voonala [86]	Case report	50 y/M	Flecainide, dose NR Oral ingestion (5.89 mcg/mL) (cardizem, aripiprazole)	0.55	Hypotension Wide QRS, QT 700 ms Cardiac arrest Single seizure Coma	NR	NR	NR	Sodium bicarbonate, IV fluids	ILE did not appear to affect the outcome	Died
Watt et al. [87]	Case Series, No 1	Young/F	Quetiapine 4.3 g Oral ingestion (diazepam 300 mg, acetaminophen (paracetamol)/dihydrocodeine, ferrous fumarate)	1.82	Coma	20%	NR	(reports: Standard lipid rescue protocol)	NR	No	Survival
	Case series, No 2	Middle-aged/F	Quetiapine 4.6 g Oral ingestion Acetaminophen (paracetamol)	1.82	Hypotension Sinus tachycardia 120 beats/min, QTc 550 ms Coma	20%	NR	(reports: Standard lipid rescue protocol)	IV fluids, Acetylcysteine	No	Survival

(continued)

Appendix 3. Continued

Article	Study type	Age/sex	Drug, dose and route [Quantitative drug concentration] (coingestant)	Log D ^c	Symptoms	ILE used	ILE bolus dose ^a	ILE infusion dose (total dose) ^b	Other treatments received	ILE effect	Outcome
Yesilbas et al. [88]	Case report	8 y/M	Organophosphate (from eating leeks) Oral ingestion	NA	Bradycardia Coma	20%	NR	8 g/kg/day for 2 days (total: 16 g/kg)	Atropine, Pralidoxime, CWHHD	No immediate improvement and other treatments given. Improved over 4 days	Survival

ACLS: Advanced cardiac life support; ARDS: Acute respiratory distress syndrome; BP: Blood Pressure; CWHHD: Continuous Venovenous Hemodialysis; ECMO: Extracorporeal membrane oxygenation; ER: Extended release; HDI: High dose insulin; HD: Hemodialysis; HIET: High-dose insulin euglycemia therapy; ILE: Intravenous lipid emulsion; MARS: Molecular Adsorbent Recirculation System; MAP: Mean arterial pressure; NA: not applicable; NR: Not reported; MSR: Normal sinus rhythm; PEA: Pulseless electrical activity; PMVT: Polymorphic ventricular tachycardia; PVC: Premature ventricular contractions; ROSC: Return of spontaneous circulation; RSI: Rapid sequence induction; TdP: Torsade de pointes; VA: Veno-arterial; YES: Ventricular extrasystoles; VT: Ventricular tachycardia.

^aThe total dose in g/kg was infrequently available, and could only be calculated if body weight was reported.

^bAvailable as abstract only at the time of writing.

^cAdapted from www.chemspider.com. The log D refers to the logarithm of octanol/water partition coefficient.

^dIndividual patient details are not reported for the case series.

^eFull text article included as it is available at the time of writing, and includes more information compared to abstract reference included in the systematic review (5).

^fThese doses are likely in mL/kg but are transcribed as reported in the original article.

Appendix 4. Summary of the 11 animal studies included in the 2015 update.

Article (Species)	Model	Poison, dose and route	Log D	Symptoms	ILE used	ILE bolus ^a	ILE infusion	Study arms	Timing of rescue, time from LA termination	Other treatments received ^b	Parameter measured	Outcome	Support effect of ILE
<i>Local anesthetics</i>													
RCS													
Udelsman [33] (Pigs)	Randomized trial	Bupivacaine 5 mg/kg Intravenous	2.68	Fall in arterial BP, and ventricular systolic work index	NR	4 mL/kg	No	LCT vs LCT/MCT vs Saline	Study treatments 1 min after LA	NR	Arterial BP, CI and ventricular systolic work index	Survival NR	Yes; Both lipid emulsions were efficient and similar options to reverse hypotension
Zaballos [34] (Pigs)	Randomized trial	Bupivacaine 4–6 mg/kg Intravenous	2.68	150% increase in QRS	20%	1.5 mL/kg	0.25 mL/kg/min Time NR	ILE vs Saline (details NR)	NR	NR	QRS	Survival: ILE 6/6 Saline 6/6	Yes; But control group QRS was wider
<i>Non-local anesthetics</i>													
RCS													
Bourque [35] (Rats)	Controlled trial	Propofol 10 mg/kg Intravenous	3.88	Hypotension	NR	4 mL/kg	No	ILE vs Saline	NR	NR	MAP, cortical activity assessments by EEG	Survival rate NR ILE superior to saline in the reversal of decreased MAP with minimal effect on the anesthetic profile of propofol	Yes
Peacock [39] (Cats)	Randomized trial	Permethrin, dose NR Topical	6.47	Some had single seizures	20%	No	15 mL/kg in 60 min	ILE vs Saline	Variable	Supportive, details NR Methocarbamol for seizure-like activity, diazepam	Authors graded the cats' neurologic status and found a decrease in the seizure-like activity, time and severity of poisoning in the treatment group	Survival: ILE NR/20 Saline NR/14	Yes; ILE-treated cats improved earlier compared to control cats
Vamey [42] (Pigs)	Randomized trial	Diphenhydramine 1 mg/kg/min Intravenous	1.92	Diphenhydramine dosing continued until MAP was 60% of baseline	20%	7 mL/kg	0.25 mL/kg/min	ILE vs Bicarbonate	Other treatment and study treatment immediately after diphenhydramine	Bicarbonate: 2 mg/kg plus an equal volume of normal saline solution	systolic BP, MAP, cardiac output, QRS and time to death	Survival: ILE 1/12 Bicarbonate 2/12	No; no difference in outcome measures between groups
<i>Case Reports/Series</i>													
Ceccherini [36] (Cats)	Case series (N = 4)	Permethrin, dose and route NR	6.47	Muscle fasciculations and seizures	NR	Variable doses	Variable doses	NA	NR	Dexmedetomidine, dose NR	NR	Survival: 4/4	Yes; seizure-like activity responded
Herring [37] (Dogs)	Case series (N = 3)	Naproxen 2.2–2.5 g Oral ingestion	0.45	NR	20%	2 mL/kg	0.25 mL/kg/min for 30 min	NA	NR	NR	NR	Survival: 3/3	The animals were empirically treated due to the high dose and it is impossible to infer any clinical benefit over supportive care alone
Jourdan [38] (Cats)	Case series (N = 20)	Ivermectin 4 mg/kg Subcutaneous	5.76–6.21	NR	20%	1.5 mL/kg (N = 16) and other ILE boluses given until clinical resolution complete	0.25 mL/kg/min for 30 min (following the bolus in N = 4 animals)	NA	Early initiation	NR	NR	Survival: 20/20	The animals were empirically treated due to the high dose and it is impossible to infer any clinical benefit over supportive care alone

(continued)

Appendix 4. Continued

Article (Species)	Model	Poison, dose and route	Log D	Symptoms	ILE used	ILE bolus ^a	ILE infusion	Study arms	Timing of rescue, time from LA termination	Other treatments received ^b	Parameter measured	Outcome	Support effect of ILE
Saïqib [40] (Lion)	Case report	Ivermectin 3 mg/kg Oral ingestion	5.76–6.21	Hypotension Bradycardia 50–60 beats/min Ataxia, apparent hallucinations, single seizure Coma Blindness Bradypnea 10–15 breaths/min Decreasing body temperature	20%	1st dose: 1.5 mL/kg 1st dose: 0.25 mL/kg/min for 30 min 2nd dose: 0.5 mL/kg/min for 30 min	NA	1st ILE dose after app. 72 h 2nd ILE dose after 92 h	IV fluids Activated charcoal and later gastric lavage Glucose, diazepam, atropine, neostigmine, ceftriaxone Mechanical ventilation	NR	Survival	Yes	
Seitz [41] (Cat)	Case report	Permethrin, dose NR Topical	6.47	Single seizure	20%	1.5 mL/kg	0.25 mL/kg/min for 2 h (total: 31.5 mL/kg)	NA	NR	IV fluids Methocarbamol, diazepam	NR	Survival; seizure termination prior to ILE persistent gross lip-emia and suspected corneal lipidosis	Yes
Williams [43] (Dog)	Case report	Synthetic cannabinoid receptor agonist	NR	Bradycardia 60 beats/min Coma Periodic apnea Hypothermia 32.5 °C	20%	1.5 mL/kg	0.5 mL/kg/h for 6 h (total: 2 mL/kg)	NA	NR	IV fluids Supportive care Mechanical ventilation	Vital parameters Drugs measured: 9-THC, AM-2201, JWH-122	Survival; mental status improved following ILE	Unclear

^aThe bolus dose in g/kg and infusion dose in g/kg/h could only be calculated if lipid concentration was reported.

^bDrugs used for general anesthesia or euthanasia are not included.

BP: Blood pressure; Ct: Cardiac index; EEG: electroencephalography; ILE: Intravenous lipid emulsion; IV: Intravenous; LA: Local anesthetic; LCT: Long chain triglyceride; MAP: Mean arterial pressure; MCT: Medium chain triglyceride; NA: Not applicable; NR: Not reported; RCS: Randomized controlled studies.

Appendix 5. Vote results

Toxins	Cardiac arrest	Life-threatening toxicity			Non-life-threatening toxicity		
		As first line therapy	As part of treatment modalities	If other therapies fail (in last resort)	As first line therapy	As part of treatment modalities	If other therapies fail (in last resort)
<i>Local anesthetics</i>							
Bupivacaine	Recommended (M:7, LQ:7, DI:0.2)	Neutral (M:6, DI:0.5)	Suggested (M:7, LQ:6, DI:0.2)	Recommended (M:8, LQ:7, DI:0.2)	Neutral (M:5, DI:0.5)	Neutral (M:5, DI:0.5)	Neutral (M:6, DI:0.5)
All other local anesthetics	Neutral (M:6, DI:0.3)	Neutral (M:5, DI:0.4)	Neutral (M:6, DI:0.5)	Suggested (M:7, LQ:6, DI:0.4)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:1.0)	Neutral (M:6, DI:0.3)
<i>Non-local anaesthetics</i>							
Antidysrhythmics Class 1	Neutral (M:5, DI:0.3)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0)	Neutral (M:6.5, DI:0.5)	<i>Not suggested</i> (M:3, UQ:5, DI:0.7)	Neutral (M:5, DI:0.6)	Neutral (M:5, DI:0.4)
Amitriptyline	Neutral (M:6, DI:0.5)	<i>Not suggested</i> (M:2.5, UQ:4.5, DI:0.3)	Neutral (M:5, DI:0.5)	Suggested (M:7, UQ:5, DI:0.4)	<i>Not recommended</i> (M:1, UQ:2, DI:0.1)	<i>Not suggested</i> (M:3, UQ:4, DI:0.5)	Neutral (M:5, DI:0.8)
Other tricyclic antidepressants	Neutral (M:5.5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.9)	Neutral (M:6, DI:0.6)	<i>Not suggested</i> (M:1, UQ:4, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	<i>Not suggested</i> (M:3, UQ:5, DI:0.8)
Baclofen	Neutral (M:5, DI:0.1)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:0)	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.7)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0.7)
Beta receptor antagonists (lipid-soluble)	Neutral (M:6, DI:0.3)	Neutral (M:4, DI:0.4)	Neutral (M:5, DI:0.3)	Neutral (M:6, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0.6)
Beta receptor antagonists (Non lipid-soluble)	Neutral (M:5, DI:0.5)	<i>Not suggested</i> (M:2, UQ:4, DI:0.5)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:1, UQ:3.5, DI:0.2)	<i>Not suggested</i> (M:1, UQ:5, DI:0.8)	Neutral (M:5, DI:0.8)
Bupropion	Neutral (M:6, DI:0.5)	<i>Not suggested</i> (M:2, UQ:5, DI:0.4)	Neutral (M:5, DI:0.4)	Suggested (M:7, LQ:5, DI:0.7)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:4, DI:0.8)	Neutral (M:5, DI:0.8)
Calcium channel blockers	Neutral (M:6, DI:0.5)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.1)	Neutral (M:6, DI:0.1)	<i>Not suggested</i> (M:1, UQ:4, DI:0.5)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0.7)
Diltiazem and verapamil	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.5)	Neutral (M:5, DI:0.2)	Neutral (M:6, DI:0.5)	<i>Not suggested</i> (M:1, UQ:4.5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)
Dihydropyridines	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.5)	Neutral (M:5, DI:0.7)	Neutral (M:6, DI:0.4)	<i>Not suggested</i> (M:1, UQ:3.75, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.8)
Cocaine	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:1, UQ:4, DI:0.2)	Neutral (M:5, DI:0.4)	Neutral (M:6, DI:0.6)	<i>Not recommended</i> (M:1, UQ:2, DI:0.1)	<i>Not suggested</i> (M:1, UQ:4, DI:0.2)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)
Diphenhydramine	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ivermectin	Neutral (M:5, DI:0)	Neutral (M:4.5, DI:0.7)	Neutral (M:5, DI:0)	Neutral (M:5, DI:0.4)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.8)	Neutral (M:5, DI:0.7)
Other insecticides	Neutral (M:5, DI:0)	<i>Not suggested</i> (M:3, UQ:5, DI:0.8)	Neutral (M:5, DI:0.3)	Neutral (M:5, DI:0.4)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:4, DI:0.7)	Neutral (M:5, DI:0.4)
Lamotrigine	Neutral (M:6, DI:0.4)	<i>Not suggested</i> (M:3, UQ:5, DI:0.8)	Neutral (M:5, DI:0.4)	Neutral (M:6.5, DI:0.4)	<i>Not suggested</i> (M:1.5, UQ:5, DI:0.5)	<i>Not suggested</i> (M:3, UQ:5, DI:0.8)	Neutral (M:5, DI:0.8)
Malathion	Neutral (M:5, DI:0)	<i>Not suggested</i> (M:3, UQ:5, DI:0.7)	Neutral (M:5, DI:0.1)	Neutral (M:5, DI:0.2)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:4, DI:0.6)	Neutral (M:5, DI:0.3)
Other pesticides	Neutral (M:5, DI:0.1)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0)	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.5)	Neutral (M:5, DI:0.8)	Neutral (M:5, DI:0.5)
Olanzapine	Neutral (M:5, DI:0.3)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:0.1)	Neutral (M:5, DI:0.4)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:0.7)
Other antipsychotics	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:3, UQ:5, DI:0.7)	Neutral (M:5, DI:0)	Neutral (M:5, DI:0.4)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:0.6)
Selective Serotonin Reuptake Inhibitors	Neutral (M:5, DI:0.1)	Neutral (M:4, DI:0.8)	Neutral (M:5, DI:0.1)	Neutral (M:5, DI:0.3)	<i>Not suggested</i> (M:2, UQ:5, DI:0.8)	Neutral (M:5, DI:0.7)	Neutral (M:5, DI:0.6)

M: Median; LQ: Lower quartile; UQ: Upper quartile; DI: Disagreement index; N/A: not applicable.