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Systematic Review

Could Intravenous Lipid Emulsion Improve the Level of Consciousness in Acute Sedative and Antipsychotic Poisoning? A Review of Randomised Human Trials

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Abstract: Introduction: Sedative and antipsychotic (SAP) agents are amongst the most common overdoses seen clinically, with few available antidotes. The proposed "lipid shuttle" mechanism of action for intravenous lipid emulsion (ILE) could augment the redistribution of SAP agents from the central nervous system in overdoses. We reviewed randomised controlled clinical trials to evaluate the effect of intravenous lipid emulsion when the indication for use was a reduction in the level of consciousness in SAP overdoses. **Methods:** We searched for human randomized controlled trials comparing the use of ILE to placebos in SAP drug overdoses. Animal and non-randomised human studies were excluded. Relevant databases were searched with two independent reviewers assessing studies for inclusion and risk of bias using the ROB 2 tool. **Results:** Five identified studies enrolled 270 patients in total, of whom 226 had isolated tramadol or clozapine toxicity. One study was assessed as having serious concerns for bias, and the other four as having some potential for bias. In all studies, there was a statistically significant increase in the Glasgow Coma Scale (GCS), favouring the ILE groups. This effect does not appear to have been due to changes in haemodynamics. Secondary outcomes on length of stay and QT interval were also positive. No patient died in any study. **Conclusions:** In the five reported randomised human trials of the effect of ILE on level of consciousness post-SAP overdose, patients receiving ILE had a greater increase in GCS over time. The potential for bias existed in all studies, and trial results may be true but specific to the intoxicants and situations studied, which prevents the generalisability of findings. More research is both feasible and necessary in this area.

Keywords: intravenous lipid emulsions; poisoning; antidotes

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1. Introduction

1.1. Why This Problem Is Important

Sedative and antipsychotic (SAP) agents are amongst the most common overdoses seen in clinical practice [1,2]. There is currently no specific antidote to manage the sedation caused by many of these agents and management is largely supportive [3–7]. While mortality is generally low, the management of comatose and stuporous patients after SAP overdose consumes significant healthcare resources. After a recent trial suggesting better outcomes in the absence of definitive airway management [8], it is possible that a greater proportion of this care may be delivered in Emergency Departments. It would be beneficial to identify adjuncts to the supportive care provided, which may optimise treatment and have a positive impact on resource demands.

1.2. Why Might ILE Work

Intravenous lipid emulsion (ILE) is an antidote recommended in the management of local anaesthetic systemic toxicity [9]. Proposed mechanisms for the action of lipid emulsion include augmentation of cardiac contraction through enhanced metabolism, reduction in vasodilatation through actions on nitric oxide, reversal of sodium channel antagonism, and a "lipid shuttle" effect [10]. The lipid shuttle describes the action of ILE to increase the blood carriage of an intoxicant with subsequent effects on redistribution, which may favour movement from a site of toxicity, such as the brain, to pharmacologically inert sites, such as adipose tissue. There is both preclinical and clinical trial evidence that ILE can augment the redistribution of agents which lead to depression of consciousness. Lipid emulsion has been demonstrated to reduce brain concentrations of amitriptyline when ILE was administered after intravenous administration and distribution of amitriptyline in pigs [11]. ILE has also been shown to augment reversal from volatile anaesthesia and reduce thiopentone-induced respiratory depression in rats [12,13]. In a randomised trial of patients undergoing isoflurane anaesthesia for laparoscopic cholecystectomy, ILE improved the anaesthetic recovery time and quality [14]. The "lipid shuttle" could theoretically improve the level of consciousness in SAP overdose patients. It should be noted that the effects of the lipid shuttle may not always be favourable. Animal studies have demonstrated increased mortality when lipid emulsion is given very early following enteric overdose, presumably through augmentation of drug absorption [15,16].

1.3. Previous Literature

Lipid Emulsion Work Group Review-2016.

A 2016 review of all available animal and human literature [17] noted a prospective case series of 30 patients where ILE was used primarily to manage CNS depression [18]. While increases in the level of consciousness were seen over time, the variability in ILE dose and non-controlled methodology meant conclusions could not be drawn. In a retrospective review of 10 cases where ILE was used for CNS depression, including six cases of quetiapine overdose, no improvement was noted after ILE [19]. Accumulated case reports in the review showed varied changes in trajectory following ILE treatment, including improvement, transient improvement and death.

An animal trial of ILE in intravenous haloperidol toxicity in rabbits noted a slight improvement in neurologic function, but increased mortality [20]. In an animal model of intravenous tramadol toxicity, rabbits treated with ILE had a reduced rate of seizures and reduced mortality [21].

One human randomised controlled trial (RCT), albeit with many identified methodological issues, reported a small difference in the increase in GCS following sedative overdose [22].

Evidence-based recommendations from 2016 recommend ILE only in local anaesthetic systemic toxicity and suggest use in a small number of toxicities where cardiovascular toxicity poses an imminent threat to life and other treatments have failed. Based on the available literature, the 2016 lipid emulsion workgroup made the suggestion not to use lipid emulsion in the first line of therapies for non-life-threatening toxicity from olanzapine and other antipsychotics [23].

Literature excluding RCT's post-2016.

Since the 2016 review, there have been a number of case reports of ILE use in SAP overdose in both sole and mixed overdoses involving quetiapine, olanzapine, and trazodone [24–32]. Outcomes in many cases were positive, though the potential for publication bias exists, and the indication for use was often haemodynamic collapse rather than altered conscious state.

A recent review of case reports and cohort data on the use of ILE in neuropsychiatric drug toxicity comprehensively summarised and analysed all of this literature [33]. Sixty ILE treatments were included, with the most common indication being haemodynamic collapse refractory to standard resuscitative measures (53 of 60 treatments). The authors concluded that ILE use was temporally associated with an improvement in QT interval and level of consciousness. While supportive of the role of ILE in neuropsychiatric drug toxicity, these data have issues with potential publication bias and lack of controls for comparison. The preponderance of haemodynamic collapse as the indication for ILE in this literature also left relatively unaddressed the question of whether ILE is useful when sedation is the major feature of toxicity.

A 2017 pharmacokinetic trial on the fate of orally dosed paliperidone in rats found a decreased tissue-to-plasma concentration ratio in the heart and brain in ILE-treated rats [34].

1.4. Our Research Question

We sought to review and analyse randomised controlled human trials to answer the question "in patients post SAP overdose where reduced consciousness is the indication for ILE use, what is the effect of intravenous lipid emulsion on consciousness level?"

2. Methods

We used a systematic review methodology to investigate the effect of intravenous lipid emulsion on consciousness level in acutely poisoned patients following SAP overdose. The systematic review followed the guidance of the Cochrane Handbook for Systematic Reviews of Interventions. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework. The review was registered with Open Source Framework (Registration DOI https://doi.org/10.17605/OSF.IO/AVUDB) prior to the commencement of work [35].

2.1. Criteria for Considering Studies in This Review

Types of studies: We searched for all English-language randomized controlled trials comparing the use of intravenous lipid emulsion to placebo in SAP drug overdose.

Types of participants: Human patients who had taken an SAP drug overdose and presented to the emergency department with reduced GCS. We excluded studies that recruited patients who had suffered from local anaesthetic drug toxicity or organophosphate poisoning. We excluded animal trials and non-randomised human studies.

Types of interventions: Intravenous lipid emulsion used during SAP drug overdose, alone or in combination with standard treatment (e.g., supportive treatment), compared with placebo, no intervention, or standard treatment alone.

Outcome measures: The primary outcome measure was improvement in GCS. The Glasgow Coma Scale is an ordinal scale that describes a patient's consciousness level, where a higher value indicates a greater consciousness level. This value was extracted from the results of the included studies.

Data were also extracted on pulse rate, systolic blood pressure (SBP) and QTc interval where reported. Adverse effects listed as associated with ILE use in a systematic review were noted [36]. These adverse effects were acute kidney and lung injury, cardiac arrest, ventilation–perfusion mismatch, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circulation machine circuit obstruction, allergic reaction, and increased susceptibility to infection.

2.2. Search Methods for Inclusion of Studies

Electronic searches: The electronic search strategy was developed based on the inclusion and exclusion criteria and then refined and cross-validated against a set of known studies in the field. The search was restricted from 1990 until 2024. We searched the following databases:

- Ovid Embase
- Ovid MEDLINE
- Pubmed
- Scopus
- Cochrane CENTRAL via CRS

2.3. Search Strategies

Search strategies are documented in depth in Appendix A.

Manual search: We also performed a manual search through 16 toxicology journals.

Search for unpublished studies: The clinical registries ClinicalTrials.gov and the World Health Organisation's International Clinical Trials Registry Platform were searched with the search terms "poisoning" and "lipid emulsion".

Selection of studies: Records were managed with the Zotero version 7 and Rayyan software (https://www.rayyan.ai/, last accessed 29 December 2024). Studies were deduplicated and selected for data extraction on Rayyan. The Rayyan software was used to facilitate independent screening and blinding of reviewer decisions. A two-independent reviewer (RH and AK) screening process was utilized for both the title/abstract screen as well as full text screening. All titles, abstracts, and full texts were screened by the same reviewers. Any disagreement between reviewer decisions was resolved by a third independent reviewer (JK).

2.4. Data Extraction

The outcome of interest, the Glasgow Coma Scale score, was extracted from the selected records by two independent reviewers (RH and JK). A quantitative meta-analysis was planned, with the effect measure of the meta-analysis being a standardized mean difference in change in the Glasgow Coma Scale score. Secondary outcomes collected were hospital length of stay and corrected QT interval.

2.5. Assessment of Risk of Bias in Included Studies

The risk of bias in the selected records was assessed using the Risk of Bias 2 (RoB2) tool. Two reviewers independently completed the risk of bias assessment of the eligible studies (AK and DC). Discrepancies in the reviewers' decisions were resolved by a consensus-based discussion involving a third reviewer (GC).

3. Results

A PRISMA diagram describing the results of the search and selection process is presented below in Figure 1.

270 patients were randomised, with 135 patients receiving ILE. Bibliometrics and baseline data from the studies are provided in Table 1. Data in all tables are presented as either means +/− standard deviation or medians (interquartile range).

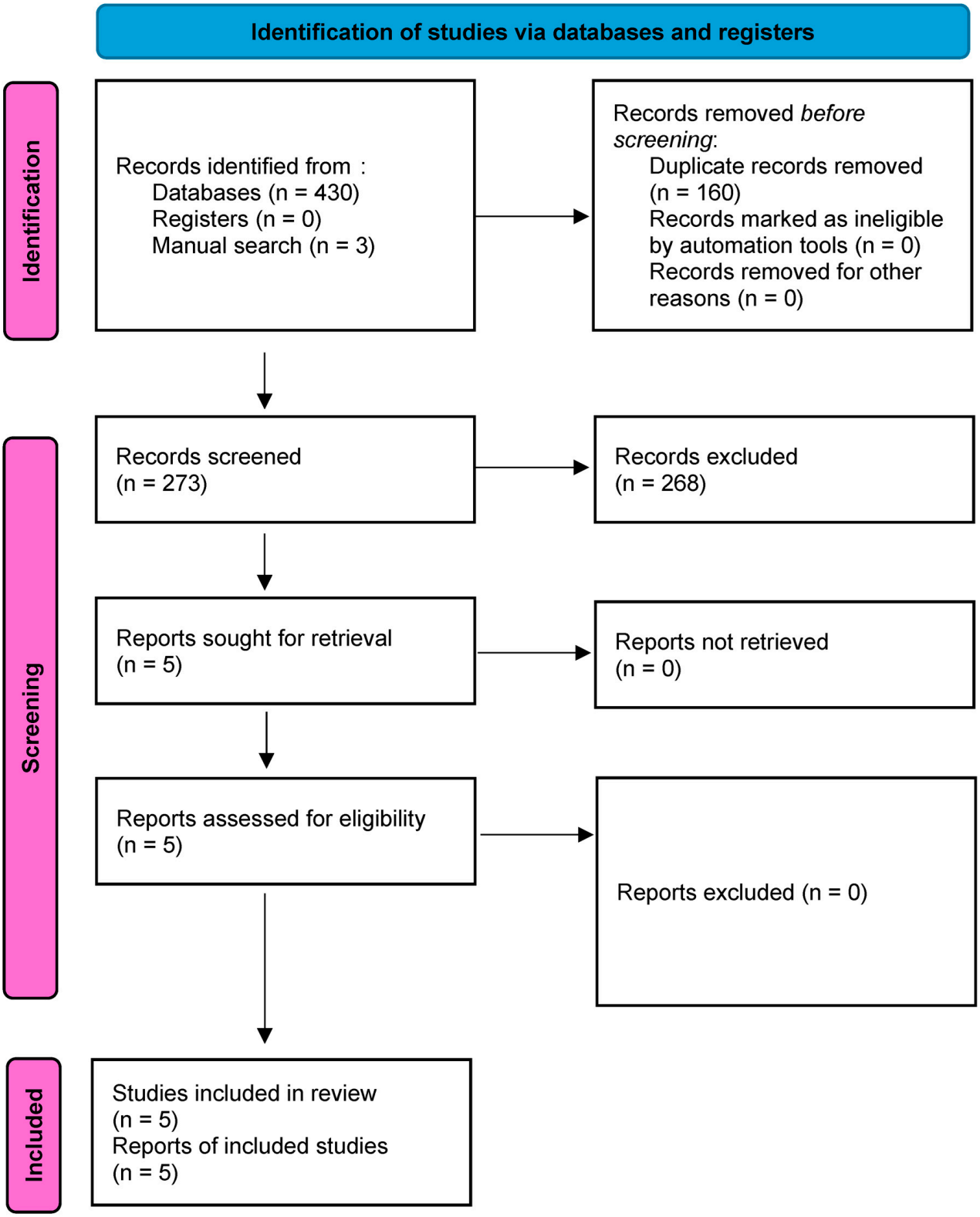


Figure 1. Prisma flow diagram [37] of the search and selection process.

Table 1. Included studies.

Authors/Year	Journal	Database	Drug/s	N	Male	ILE Age (Years)	Control Age (Years)	Control	Post OD to ED ILE (h)	Post OD to ED Control (h)	ILE Given
Taftachi et al. 2012 [22]	European Review of Medical and Pharm. Sciences	Pubmed	Combination *	30	18	23 ± 5	28 ± 11	Nil	n/r	n/r	10 mL/kg 10% Intralipid
Elgazzar et al. 2021 [38]	Human and experimental Toxicology	Pubmed	Clozapine	40	18	17.5 (4.5–22) **	16.5 (7–21.5) **	Nil	4(3–5)	4 (4–6)	1.5 mL/kg 20% SMOF lipid then 6 mL/kg over 1 h
Basiouny et al. 2022 [39]	Ain Shams Journal of Forensic Med. and Clin. Tox.	Hand search	Antipsychotics:***	40	17	13.5 (5–21.5) **	10 (4–18.5)	Nil	5 (3–6)	4 (3.5–6)	1.5 mL/kg 20% SMOF lipid then 6 mL/kg over 1 h
Behnoush et al. 2024 [40]	The Journal of Emergency Medicine	Pubmed	Tramadol	120	84	25.3 ± 5.4	23.2 ± 6.7	0.9% NaCl	4.7 (1.3)	4.3 (1.2)	100 mL SMOF lipid bolus followed by maximum 250 mL over 15 min
Gomaa et al. 2024 [41]	Zagazig Journal of Forensic Med. and Tox.	Hand search	Clozapine	40	17	28.8 ± 9.9	24.3 ± 6.6	Nil	2.4 (2.2)	4.3 (4.2)	1.5 mL/kg over 2 min then 0.25 mL/kg/min for 30–60 min

* Benzodiazepines, Tricyclic antidepressant, anticonvulsants, anticholinergics, antihistamines, muscle relaxants, selective serotonin reuptake inhibitors, antipsychotics, nonsteroidal anti-inflammatory drugs, opioids, salicylates; N = total number in study. ** median (interquartile range). *** Clozapine 65%, chlorpromazine (15%), haloperidol (12.5%), risperidone (5%), olanzapine (2.5%); OD = overdose. ED = Emergency Department. "Post OD to ED" represents time between ingestion and hospital presentation.

3.1. Risk of Bias Assessment

Two authors (DC and AK) performed the risk of bias assessment using the Cochrane risk of bias assessment tool. Disagreement between authors was resolved through discussion involving a third reviewer (GC). The results of the risk of bias assessment are shown in Table 2.

Table 2. Risk of bias assessment.

Paper	Randomisation	Assignment to Intervention	Adherence to Intervention	Outcome Data	Outcome Measurement	Reported Result	Overall
Taftachi et al. 2012 [22]							
Elgazzar et al. 2021 [38]							
Basiouny et al. 2022 [39]							
Behnoush et al. 2024 [40]							
Gomaa et al. 2024 [41]							

Green = low risk for bias, Orange = some concerns for bias, Red = high risk for bias.

Taftachi was assessed as having a high risk of bias, with issues with randomisation, no control nor protocolised care for controls leading to potential for differing baseline treatments based on study group allocation, unclear delineation of whether those assessing GCS knew of the group allocation, and reporting of a change rather than base parameters for GCS.

All other studies were adjudged as having some concerns for potential bias. The concerns for Elgazzar, Baisouny, and Gomaa arose from a lack of blinding, leading to potential issues with the assessment of GCS or deviations from the usual protocolised baseline treatment. While the Behnoush study was appropriately blinded, a higher rate of seizure in the control group with increased seizure treatment may have been a confounder for the level of consciousness in controls.

3.2. Reported Endpoints

3.2.1. Primary Endpoint

Glasgow Coma Scale (GCS)

For the majority of included patients, the GCS was reported as a non-parametric variable [39,40]. Cohort-level meta-analysis requires assumptions of normality, and direct contact with authors from all included studies did not yield a dataset that was able to overcome this limitation. Additional challenges were differences in timepoints of reporting and presentation of the data as both absolute value and change in different studies. As such, we did not move forward with our planned meta-analysis, and chose to tabulate and present data from individual studies.

At all timepoints when GCS was reported, there was a statistically significant increase favouring the lipid emulsion treatment groups as shown in Table 3.

3.2.2. Secondary Endpoints

Hospital length of stay was reported in four of the five included papers. In all of these papers, the lipid-treated groups had a shorter duration of hospital stay, as shown in Table 4.

QTc Interval

Two papers reported on the value of QTc. In both papers, the lipid-treated groups had lower QTc at 12 h, shown in Table 5.

Table 3. GCS at different timepoints.

Authors/Year	Baseline GCS Control	Baseline GCS Lipid	*p* Value	GCS 6 h Control	GCS 6 h Lipid	*p* Value	GCS 12 h Control	GCS 12 h Lipid	*p* Value
Taftachi et al. 2012 [22]	n/r	n/r		3 ± 1	2 ± 2 *	0.04	n/r	n/r	
Elgazzar et al. 2021 [38]	8.5 ± 2.2	8.8 ± 2	0.705	9.2 ± 2.3	13.1 ± 9.2	<0.001	9.6 ± 2	14.3 ± 1.5	<0.001
Basiouny et al. 2022 [39]	9 ± 2.7	10.1 ± 2.2	0.677	10 (8.5–11.5)	15 (12.5–15)	<0.001	14 (9–14.5)	15 (15–15)	0.006
Behnoush et al. 2024 [40]	9.5 (7–10)	10 (8–10)	0.51	n/r	n/r		10 (8–12)	12 (10–13)	0.03
Gomaa et al. 2024 [41]	5.3 ± 1.7	5.0 ± 2.1	0.56	n/r	n/r		7.25 ± 2.1	13.3 ± 1.5	<0.001

n/r = not reported; * reported as change from baseline; Data are presented either as mean ± standard deviation **or** median (interquartile range).

Table 4. Hospital length of stay.

Authors/Year	HLOS Control (h)	HLOS Lipid (h)	*p* Value
Elgazzar et al. 2021 [38]	71 (48–84)	18 (12–24)	<0.001
Basiouny et al. 2022 [39]	42 (24–72)	18 (12–24)	0.001
Behnoush et al. 2024 [40]	120(96–168) *	72 (48–120) *	0.02
Gomaa et al. 2024 [41]	68 ± 24	26 ± 8	<0.001

* reported as days in the paper.

Table 5. QTc interval.

Authors/Year	QTc Control 12 h (s)	QTc Lipid 12 h (s)	*p* Value
Elgazzar et al. 2021 [38]	0.47 ± 0.07	0.39 ± 0.02	0.001
Basiouny et al. 2022 [39]	0.48 (0.44–0.51)	0.44 (0.41–0.46)	0.011

Gomaa et al. [41] reported no significant difference in the incidence of prolonged QTc at 12 h (15% for controls and 10% for ILE-treated patients).

Pulse Rate

All papers reported the initial pulse rate, although two reported only the proportion of patients who were initially tachycardic. Of the four papers in which pulse rate was subsequently reported, three did not show any difference either over time or between groups. One in which all patients were intoxicated with clozapine showed a lower proportion of patients who were tachycardic at 12 h in patients treated with ILE. These findings are shown below in Table 6.

Table 6. Pulse rate (beats per minute).

Study	Pulse Initial Control	Pulse Intial ILE	Pulse 6 h Control	Pulse 6 h ILE	Pulse 12 h Control	Pulse 12 h ILE
Taftachi et al. 2012 [22]	97(±23)	91(±25)	98(+/−15)	91(+/−16)		
Elgazzar et al. 2021 [38]	60% tachy	70% tachy				
Basiouny et al. 2022 [39]	80% tachy	85% tachy			120 (±20)	115 (±76)
Behnoush et al. 2024 [40]	102 (±8)	105 (±10)			108 (±16)	102 (±60)
Gomaa et al. 2024 [41]	118 (±18)	117 (±11)			80% tachy *	30% tachy *

Tachy = tachycardic, defined as pulse rate > 100 beats per minute; * $p < 0.01$.

Systolic Blood Pressure

All studies reported on initial systolic blood pressure. Two studies reported on this as a percentage of patients who were hypotensive, defined as a systolic blood pressure less

than 90 mmHg. No differences between ILE and control groups were seen at any time for SBP. These findings are shown in Table 7.

Table 7. Systolic blood pressure (mmHg).

Study	SBP Initial Control	SBP Intial ILE	SBP 6 h Control	SBP 6 h ILE	SBP 12 h Control	SBP 12 h ILE
Taftachi et al. 2012 [22]	110 (±17)	109 (±11)	117 (±23)	112 (±9)		
Elgazzar et al. 2021 [38]	45% hypotensive	35% hypotensive				
Basiouny et al. 2022 [39]	45% hypotensive	35% hypotensive				
Behnoush et al. 2024 [40]	118 (±19)	130 (±20)			121 (±10)	130 (±14)
Gomaa et al. 2024 [41]	121 (±21)	115 (±11)				

Mortality

There were no deaths reported in any of the studies.

3.3. Adverse Effects

No cases of cardiac arrest, ventilation–perfusion mismatch, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circulation machine circuit obstruction or allergic reaction to ILE were reported. No differences in biochemical indices of renal function over time were observed in the single study where this was measured [22]. No differences in hepatic enzyme concentration nor platelet count over time were observed in the two studies where these were measured [39,40]. No abnormality of blood lipids was noted at the end of the observation period in the three studies where this was measured [38–40]. One study reported the incidence of pneumonia as non-significantly lower in the ILE-treated group [40].

3.4. Unpublished Studies

We were unable to locate a publication to match a study that received ethical approval in January 2022 on the effect of lipid emulsion on respiratory depression in methadone toxicity [42].

4. Discussion

In the five reported randomised controlled human trials in our review, patients receiving ILE for the indication of reduced level of consciousness had a greater increase in GCS over time relative to controls. The strength of this observation is limited by all studies having at least some concerns for bias, heterogeneity in the magnitude of the effect and potential issues around external validity. A planned meta-analysis was not undertaken as we believed the imposition of assumptions of normality on non-normally presented data was not analytically valid.

Whilst we did not a priori define secondary endpoints for this review, we reported them as findings of interest. In the four studies where hospital length of stay was reported, this was shorter for ILE-treated patients. The differences in length of stay observed were clinically meaningful, and future studies may further evaluate this as an important endpoint. In the two studies reporting QTc duration, both reported a lower QTc with ILE treatment. The objective nature of QTc makes it an attractive endpoint for future study. Behnoush also reported a lower seizure frequency in tramadol-intoxicated patients treated with ILE. Our group evaluated this study as at low risk of bias for this endpoint.

The positive observed effects for ILE in these papers are in keeping with a 2019 meta-analysis of studies of the effect of ILE in organophosphate poisoning [43], in which seven studies, all from China, demonstrated positive effects on different endpoints. Of the two subsequent RCTs, one demonstrated an effect for ILE in organophosphate toxicity

and one did not [44,45]. A 2019 laboratory-based crossover trial of the effects of ILE administered during intravenous metoprolol infusion (60 mg over 30 min) found increases in heart rate and cardiac output when ILE was administered [46]. These effects were of uncertain clinical significance. In a 2022 study in which GCS was not assessed, tramadol-intoxicated patients treated with ILE had a lower frequency of seizures than controls [47].

Current thinking on potential mechanisms for a therapeutic effect for ILE in poisoning involves both pharmacokinetic and pharmacodynamic effects. The proposed pharmacodynamic actions—cardiotonic effects on metabolism, ion channel modulation, and nitric oxide scavenging [10]—would be unlikely to augment the level of consciousness in the absence of shock. In three of the included studies, representative statistics of SBP did not suggest shock was present in patients studied [22,40,41]. In the two other studies, a substantial minority of both ILE and control patients were hypotensive [38,39]. The absence of mortality in both treatment arms suggests that shock, if present, was not severe. A further mechanistic observation is that a target therapeutic lipaemia of 1% [48] does not, even for most lipophilic intoxications, provide sufficient volume to represent a pharmacokinetic "sink" at a steady state. The observations and arguments above favour the "lipid shuttle" as the mechanism for any effects on GCS seen in studies included in this review. The "lipid shuttle" involves ILE augmenting redistribution from rapidly perfused central compartments to pharmacologically inert sites, such as the peripheral adipose. Such augmentation of distribution requires that the intoxicant contained in lipid microdroplets is not pharmacokinetically inert and can move into tissues within one circulation time. Should this process occur in distribution, it is also conceivable that it may occur during metabolism.

Clozapine was a prominent intoxicant in our review. The hepatic extraction ratio of clozapine at 20% [49] is far greater than the free fraction at 5% [50], suggesting that some protein-bound clozapine is available for metabolism. This is conceivably also the case for clozapine in ILE microdroplets. With a reported elimination half-life of 10 h [49], the reported length of stay in controls in clozapine intoxication is consistent with metabolism being the mechanism for the resolution of toxicity. The reduction in length of stay with ILE generates the hypothesis that increased blood concentrations with ILE increases hepatic delivery of clozapine, which may increase drug metabolism. A further mechanistic observation is that at physiologic pH, tramadol is not particularly lipophilic [51], with a pKD at pH 7.4 of 0.48. This suggests that any pharmacokinetic effect for ILE in tramadol toxicity is not mediated by a lipophilic interaction with soybean oil in lipid microdroplets. We suggest sequestration in the egg phosphatidylcholine droplet membrane or some as yet undiscovered pharmacodynamic action as potential mechanisms of action for ILE in tramadol poisoning.

Worse outcomes were seen with the dosing of ILE 30 min after the enteral overdose of amitriptyline in rats [15]. The authors concluded that ILE may augment absorption, thus increasing toxicity in enteral overdose. If this effect is present in humans, it was not seen in any of the metrics analysed in this review. Four of the five studies reported time to hospital presentation, and in all of these the mean or median for control patients was 4 to 5 h, after peak concentrations of orally administered clozapine and tramadol are expected [49,52]. In the one study where time to presentation was not well matched between groups, the mean time to presentation was 2 h lower for the ILE-treated patients [41], and significant improvement in GCS and tachycardia was seen for ILE patients relative to controls.

4.1. Limitations

While reported trials are positive, scepticism remains a valid viewpoint towards the effect of ILE on LOC in overdose. Potential for bias existed in all studies, particularly as in the majority of trials, assessors were not blinded to treatment allocation, and measurement of GCS has potential for subjectivity.

Studies may have issues with external validity with measured effects that may be real but intoxicant- or site-specific. Of the 270 patients studied, 226 had either isolated tramadol or clozapine toxicity, and it is conceivable that the effects seen for ILE would not generalise to other intoxications. The majority of overdoses reported had ingested a single agent and findings may not generalise to polypharmacy overdose. Lipid emulsion has been reported to potentially increase enteric absorption and worsen toxicity in experimental models [15,16]. The timing of presentation relative to absorption in the studied cohorts may be important and not reproduced in other populations.

Authors performing the risk of bias assessments regarded management as effectively protocolised if treatment had occurred in a major centre and standard care was described in the text. This was, however, somewhat subjective. Given that blinding was an issue for four of the five papers included in the review, there is potential to strengthen future work with explicit protocolisation of management.

Small studies have an inherent tendency to have a wider spread of effect, given that the standard error of the mean is proportional to the inverse of the square root of the number of subjects. This may lead to a wider spread and, thus, an overestimation of the effect from small studies such as those included in this review, particularly if combined with publication bias. The only unpublished work identified began recruitment in January 2022 but has not yet been reported.

All patients in all studies survived. A larger number of patients would need to be studied to exclude rare but severe complications of ILE, as there is no evidence for counterbalancing the therapeutic effect on mortality. No adverse effects were detected in any of the included studies. While reassuring, the upper bound for the 95% confidence interval for the incidence of adverse effects, given the total number of patients studied, is still 2.8% [53].

4.2. Future Directions

Future research may aim to strengthen the evidence base by significantly increasing the number of patients studied, ensuring adequate blinding for both treatment providers and outcome assessors, and prioritizing resource utilization metrics as endpoints. In order that a true complication rate of 1% would be 80% likely to be identified, a total of 780 patients in each group would need to be studied [54]. Behnoush et al. blinded patients and assessors at the time of treatment by use of a sleeve over intravenous tubing used in their study. In Figure 2, a photograph of 20% and 1% Intralipid® is shown. The use of dilute lipid emulsion as the control suspension could further improve blinding in future work. Behnoush et al. also noted the potential importance of ILE in improving hospital resource utilisation in resource-constrained settings. Reporting on length of stay as a primary outcome is another approach future studies may wish to consider.



Figure 2. 1% Intralipid® (**left**), 20% Intralipid (**right**).

5. Conclusions

In all of the five reported randomised human trials on acutely poisoned patients with reduced consciousness secondary to SAP overdose, patients receiving ILE had a greater increase in measured level of consciousness over time relative to controls. This effect does not appear to have been due to improvements in haemodynamics. That there was potential for bias in all studies and that results may be true but specific to the intoxicants and situations studied prevents generalisability of the findings. More research is both feasible and necessary in this area.

Author Contributions: J.K.—Review design, review realization, analysis, manuscript writing; D.C.—Analysis, manuscript writing; R.H.—Analysis, review realization, manuscript writing; A.K.—Analysis, review realization, manuscript writing; G.C.—Study conception, review realization, analysis, manuscript writing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: All data collated for this review are available from study authors on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Appendix A.1. Pubmed Search Strategy

1. ((((((overdose[Title/Abstract]) OR (toxicity[Title/Abstract])) OR (toxic*[Title/Abstract])) OR (poisoning[Title/Abstract])) OR (poison*[Title/Abstract])) OR (intoxicat*[Title/Abstract])) OR (drug overdose[MeSH Terms])
2. ((((((Lipid emulsion[Title/Abstract]) OR (fat emulsion[Title/Abstract])) OR (lipid rescue[Title/Abstract])) OR (lipid sink[Title/Abstract])) OR (intravenous* lipid*[Title/Abstract])) OR (Lipid sequest*[Title/Abstract])) OR (intralipid*[Title/Abstract])
3. ((((((((((GCS[Title/Abstract]) OR (Glasgow coma scale[Title/Abstract])) OR (Conscious*[Title/Abstract])) OR (Consciousness[Title/Abstract])) OR (alert*[Title/Abstract])) OR (Alertness[Title/Abstract])) OR (aware*[Title/Abstract])) OR (Awareness[Title/Abstract])) OR (Wakeful*[Title/Abstract])) OR (Wakefulness[Title/Abstract])) OR (Responsive*[Title/Abstract])) OR (Responsiveness[Title/Abstract])
4. #1 AND #2 AND #3

Appendix A.2. Scopus Search Strategy

(TITLE-ABS-KEY (lipid AND emulsion) OR TITLE-ABS-KEY (fat AND emulsion) OR TITLE-ABS-KEY (lipid AND rescue) OR TITLE-ABS-KEY (lipid AND sink) OR TITLE-ABS-KEY (intravenous* AND lipid*) OR TITLE-ABS-KEY (lipid AND sequest*) OR TITLE-ABS-KEY (intralipid*)) AND (TITLE-ABS-KEY (gcs) OR TITLE-ABS-KEY (glasgow AND coma AND scale) OR TITLE-ABS-KEY (conscious*) OR TITLE-ABS-KEY (alert*) OR TITLE-ABS-KEY (aware*) OR TITLE-ABS-KEY (wakeful*) OR TITLE-ABS-KEY (responsive*)) AND (TITLE-ABS-KEY (overdose) OR TITLE-ABS-KEY (toxic*) OR TITLE-ABS-KEY (poison*) OR TITLE-ABS-KEY (intoxicat*)) AND NOT (animal*).

Appendix A.3. Cochrane Library Search Strategy

(overdose OR toxicity OR toxic* OR poison* OR intoxic* OR (drug overdose)) AND (intralipid* OR (lipid emulsion) OR (fat emulsion) OR (lipid rescue) OR (lipid sink) OR (intravenous* lipid*) OR (lipid sequest*)) AND (GCS OR (Glasgow coma scale) OR (conscious*) OR consciousness OR alert* OR alertness OR aware* OR wakeful* OR responsive*).

Appendix A.4. Ovid MEDLINE and Embase Search Strategy

1. overdose.ab,kf,ti.
2. toxicity.ab,kf,ti.
3. toxic*.ab,kf,ti.
4. poisoning.ab,kf,ti.
5. poison*.ab,kf,ti.
6. intoxicat*.ab,kf,ti.
7. drug overdose.ab,kf,ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. lipid emulsion.ab,kf,ti.
10. fat emulsion.ab,kf,ti.
11. lipid rescue.ab,kf,ti.
12. lipid sink.ab,kf,ti.
13. intravenous* lipid*.ab,kf,ti.
14. lipid sequest*.ab,kf,ti.
15. intralipid*.ab,kf,ti.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. GCS.ab,kf,ti.
18. Glasgow coma scale.ab,kf,ti.

19. conscious*.ab,kf,ti.
20. consciousness.ab,kf,ti.
21. alert*.ab,kf,ti.
22. alertness.ab,kf,ti.
23. aware*.ab,kf,ti.
24. awareness.ab,kf,ti.
25. wakeful*.ab,kf,ti.
26. wakefulness.ab,kf,ti.
27. responsive*.ab,kf,ti.
28. responsiveness.ab,kf,ti.
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 8 and 16 and 29
31. (8 and 16 and 29) not (exp animals/not humans.sh.)

Appendix A.5. List of Journals for Manual Search

1. Al Ameen Journal of Medical Sciences
2. Halo 194
3. Ain Shams Journal of Forensic Medicine and Clinical Toxicology
4. Iranian journal of emergency medicine
5. BLDE University Journal of Health Sciences
6. Medical Sciences Forum
7. The Egyptian Journal of Forensic Sciences and Applied Toxicology
8. Pharmacology, Toxicology and Biomedical Reports
9. International Journal of Pharmacology and Toxicology
10. Advances in Toxicology and Toxic Effects
11. Ukrainian Journal of Modern Toxicological Aspects (aka Ukranian Journal of Modern Problems in Toxicology)
12. Zagazig Journal of Forensic Medicine and Toxicology
13. Egyptian Society of Clinical Toxicology Journal
14. Journal of Medical Toxicology and Clinical Forensic Medicine
15. Journal of Forensic Toxicology & Pharmacology
16. Advances in Clinical Toxicology

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5. Available online: https://www.toxinz.com/specifications/nonbenzodiazepine-hypnosedatives/?&name=Nonbenzodiazepines (accessed on 29 December 2024).
6. Available online: https://www.toxinz.com/specifications/antipsychotics-master/atypical-antipsychotics/?&name=Atypical%20Antipsychotics (accessed on 29 December 2024).
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